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THE
LARYNGOSCOPE.

VOL. LXVI JULY, 1956 No. 7

SYMPOSIUM.

The Operation for the Mobilization of the Stapes in Otosclerotic Deafness.

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MODERATOR.

HOWARD P. HOUSE, Los Angeles, Calif.

REMARKS.

SAMUEL ROSEN, M.D., New York, N. Y.

OPEN DISCUSSION.

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DR. PHILIP E. MELTZER: The members of the panel agree to speak extemporaneously. I do not have the facility of speaking in that manner; therefore I wrote these notes last night. Forgive me if it sounds a little didactic, but this is the only way that I can present what I have to say in a suitable manner.

I am grateful for the privilege of appearing in this symposium. I am comparatively inexperienced, though well acquainted with the history of this procedure under discussion. In this country it had its inception at the institution where I had my otological training; in fact, it was under the very man who in 1892 introduced stapes mobilization, namely, Dr. Frederic L. Jack.

His chief, Dr. Clarence Blake, also experienced in this procedure and a most erudite individual, summarized the several surgical efforts of that era to improve hearing. In this review he related the attempts by Kessel, Schwartze, Urbantschitsch, Boucheron, Miot and Gelle.

Deafness then as now occupied the minds of these great otologists. It was the deafness resulting from suppurative otitis that concerned them mostly. Chronic otitis insidiosa, as otosclerosis then was known, was vaguely understood. Politzer was perhaps one of the first to describe stapes fixation clinically as a result of a bony ankylosis. Haberman demonstrated histologically what this malady really was.

The surgical efforts in vogue from 1875 to 1888 to improve hearing may appear absurd to you in retrospect, but at that time they were considered bold and daring. The procedures began with simple incision of the membrana tympani, advancing courageously to the removal of drum membrane, malleus and incus. Then began the attack on the stapes itself, first severance of adhesions, then severance of the stapedial tendon, finally the revolutionary procedure of stapes mobilization, including stapedectomy.

Boucheron was perhaps the first actually to practice mobilization, but to Miot must go the real credit of enlightening the otologists of that period about this operation. With the ex-

ception of modern incisions to expose the tympanum he described with infinite detail the entire procedure of stapes mobilization, the indications, pitfalls and results.

To these early French and American pioneers our salute! After the initial reports of success with this operation came the years of silence. Nothing more was seen or heard about mobilization in our lifetime. Why? I can only venture a guess. It failed; hearing was not lastingly improved.

This generation is grateful for the perseverence of Holmgren, the surgical ingenuity of Sourdille and Lempert, and now for the astute observation of Rosen, and once again to Lempert. Why Lempert again? Ask yourself, would the tympanum be exposed so beautifully without his incision for tympanoplexy?

To Rosen must go the credit of rediscovery of stapes mobilization. Rosen's recent technique has definitely given otologists a new enthusiasm.

You have observed that I have refrained from quoting figures for immediate, temporary or late results. I have too vivid a recollection of my humble early results with the fenestration operation to do so, and I am too old a hand to sound off prematurely; furthermore, what difference does it make what these early results were? Does it matter if three or four patients are improved by stapes mobilization in ten attempts? Are not three or four successes a real attainment? Given time and experience and understanding as to why we fail, should we not expect better results just as we improved our results with the fenestration operation? I believe so.

I am too affectionately involved with the fenestration operation to ever abandon for a moment my first love. I would be negligent in my duty if I were not progressive enough to adopt a procedure, the success of which my own eyes have witnessed.

The hearing improvement brought about by stapes mobilization is of such magnitude that I confidently look forward to its becoming as firmly established a procedure for the improvement of hearing in otosclerosis as the fenestration operation.

We acknowledge Dr. Rosen's contribution regardless of whether my prophecy proves to be correct.

DR. HOUSE: Thank you very much. I think it is very apropos to review the historical developments that led up to our modern clinical surgery in the treatment of otosclerosis. I will ask Dr. John Lindsay to discuss with you some of the histopathological activities which occur in and about the footplate and which influence the stapes mobilization procedure.

DR. JOHN R. LINDSAY: Dr. Anson has demonstrated the development of the normal stapes in the human. In my part of this symposium I wish to illustrate mostly by slides some of the problems that are presented by otosclerosis as it causes fixation of the footplate. There are two ways in which one may observe the effect of otosclerosis at the joint: one is by direct observation at the time of operation; the other and more effective way is to study the microscopic sections cut through the stapes and the joint. In our collection of otosclerotic material there are not many cases of stapes fixation; therefore, it seemed best if I mentioned the literature freely to illustrate to you some of the different ways in which the joint may be attacked. I have selected illustrations by Guild, Eggston and Wolff, Lempert's collection, Nager and Meyer, Anson and Bast, some of our own, and perhaps one or two others.

The first slide is from an illustration from Dr. Guild which illustrates certain points. Three sections are shown from a case with fixation of the stapes where there was a hearing loss of about 55 db in speech frequencies. It illustrates several factors: one is the approximate comparison of the thickness of the crus with the footplate of the stapes in the part where it is affected by the disease. If you look at a section like this, you may not get a reliable idea of how firmly fixed that stapes may be; you see the ankylosed part in only one dimension. In this case Dr. Guild stated that the fixation occupied the posterior part of the joint instead of the anterior, which is usually involved, and the entire posterior third of the circumference of the joint between the footplate and the labyrinthine capsule was involved; hence this would probably be a difficult case to

mobilize, if you were dependent upon the stress which could be applied through the crura from the head or neck.

Dr. Rosen illustrated a group of 50 normal stapes, in one or two of his articles, which gives an idea of the variations in the normal. The next illustration is one of Lempert's collection showing a diseased stapes. Presumably this shows otosclerotic involvement of one crus of the stapes and gives some idea of how the strength of one crus or perhaps both crura might be reduced by the disease.

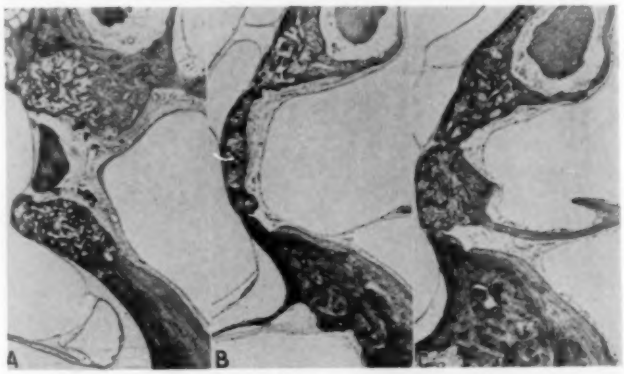

Fig. 1. From Guild, Stacy R., Ph.D.: Histologic Otosclerosis. Annals of Otology, Rhinology and Laryngology, 53:246-266, 1944. A, B and C are, respectively, photomicrographs of vertical sections through the anterior, middle and posterior thirds of the oval window of the left ear. This otosclerotic area was actively growing and had formed osseous connections with the stapedial footplate in three regions, two of which are shown. See Test. Aut. No. 10692.

It is a clinical observation that in some cases of early fixation or with a moderate degree of deafness from otosclerosis there may be slight mobility of the stapes when you first touch it with an instrument. The question is whether the fixation is all bony or is it partly fibrous. This illustration is from Dr. House's case which was reported a few years ago. It was successfully fenestrated, but on microscopic examination when the case came to termination a few years later we were unable to find any definite bony fixation. This suggested that the degree of fibrosis at the joint may be partly responsible for the

impairment of hearing and for the fact there may be slight movement in some of these cases. There is a possibility, of course, that during fenestration the removal of the incus may have loosened the stapes.

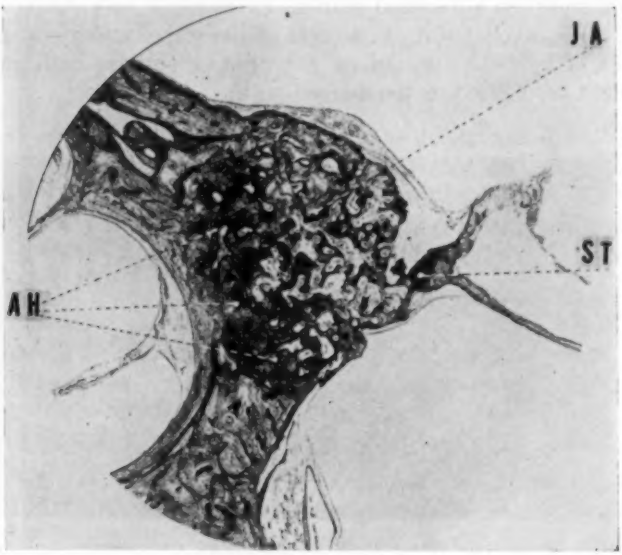

Fig. 2. From Nager, F. R., and Meyer, Max: Beiträge zur normalen und pathologischen Histologie der knöchernen Labyrinthkapsel. Passow-Schaefer, Beiträge Bd. 30 (1932) (Abb. 65. Fall 46. 3½ year old boy. Page 235). Magnification ×20. H. & E. stain. Active part of the focus (JA) at the margin of the oval window niche with extension to the stapes (ST). Older part of the focus (AH) in the form of compact "Breccie" at some distance from the niche. Sharp demarcation from the primary labyrinthine bone.

This next illustration shows a thin, well sclerosed bridge of bone producing the ankylosis. When viewed in this plane alone it would look like an ideal case for mobilization; perhaps it is, but one section does not give a complete picture. From this section alone one does not know how extensive the ankylosis may be around the circumference of the joint. This picture also gives only a partial idea of the relative strength of the crus as compared to the strength of the footplate. The

footplate is a broad structure, relatively thin but broad, and may be stronger than it would appear on this view; also the crus may be broader in one dimension and, therefore, stronger than it appears here.

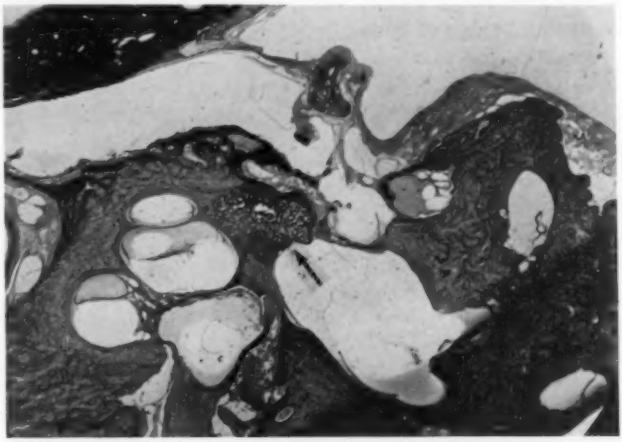

Fig. 3. From House, Howard P., Perret, Pierre and Lindsay, John R.: Histologic Observations on Fenestrated Human Ears. Part II. Otosclerosis: Two Years Following Fenestration. Supplement to the Transactions of the American Academy of Ophthalmology and Otolaryngology, July, 1951. Given before the Otosclerosis Study Group, October 7, 1950. Horizontal section through the cochlea and stapes footplate, between which is seen a large focus of otosclerotic bone (arrow). Stapes ankylosis is not present.

(Slide) These next two illustrations again showing fixation are taken from Bast and Anson's book. I call your attention to the point with which everybody has been concerned, how long a stapes is going to remain mobile after it has been mobilized. Many people, including myself, have been surprised with the length of time that they may remain mobile. Perhaps it is in the case that, with a well sclerosed bridge of bone, when it is broken loose there may be a longer period of freedom from reankylosis. On the other hand, as you see in some later slides, if an active focus extended across the joint and produced the fixation one might expect to get an earlier reankylosis. There may be practical significance to a very strong Schwartze's sign, as our best clinical indication of activity

around the joint. Such a case might not be so good for mobilization as one in which there was no activity, and the ankylosis was of sclerotic bone.

(Slide) In this next case the ankylosis is formed by a thick bridge of bone. It illustrates the comparative thinness of one crus and how easily a crus might be broken in trying to break loose such a bridge of bone.

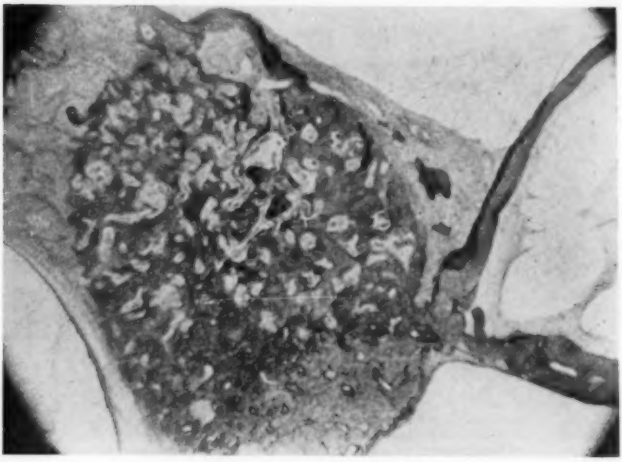

Fig. 4. From Eggston, Andrew A. and Wolff, Dorothy: Histopathology of Ear, Nose and Throat. Williams and Wilkins Co., Baltimore, 1947, p. 456, Fig. 278. Otosclerosis as seen in H and E stain showing the differentiation between normal and pathological bone. Note ankylosis of the footplate of stapes and the flecks of calcium deposited in the scar tissue lying between the crus and the cochlear wall.

(Slide) The illustrations to follow represent rather extensive cases of otosclerosis, advanced cases. It is, therefore, doubtful whether cases like these might come up for mobilization since a severe hearing loss might be expected. In this case you can see an active focus spreading across the footplate, and you see also the thin crus. You can understand the difficulty in mobilizing such a footplate if you were depending upon the force that you could apply by way of the head or neck transmitted through the crura. In more advanced cases it may

be necessary to have some means by which the footplate can be mobilized directly, if we hope to have success.

(Slide) I call your attention to the visibility of the footplate of the stapes. In a horizontal section through the temporal bone, through the stapes, one gets the impression that the

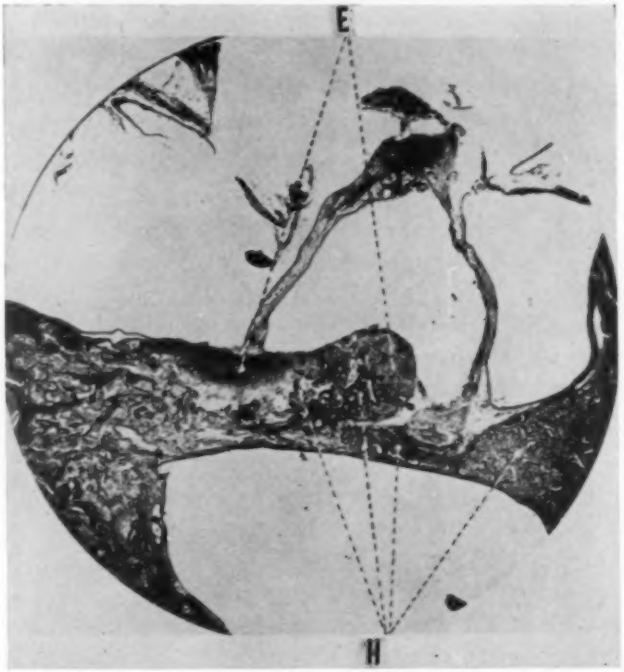

Fig. 5. From Nager, F. R., and Meyer, Max: Beiträge zur normalen und pathologischen Histologie der knöchernen Labyrinthkapsel. Passow-Schaefer, Beiträge Bd. 30 1932 (Abb. 63. Fall 27. p. 231). Magnification ×13. H & E stain. Submucosal exostosis (E) extending over the oval window from its anterior border. An otosclerotic focus (H) extends from behind over the stapes footplate into the exostosis.

stapes footplate would be easily visualized. Another point illustrated here is a dehiscence of the bony canal for the facial nerve in proximity to the posterior crus. It would be quite easy to injure the nerve in the middle ear portion where it

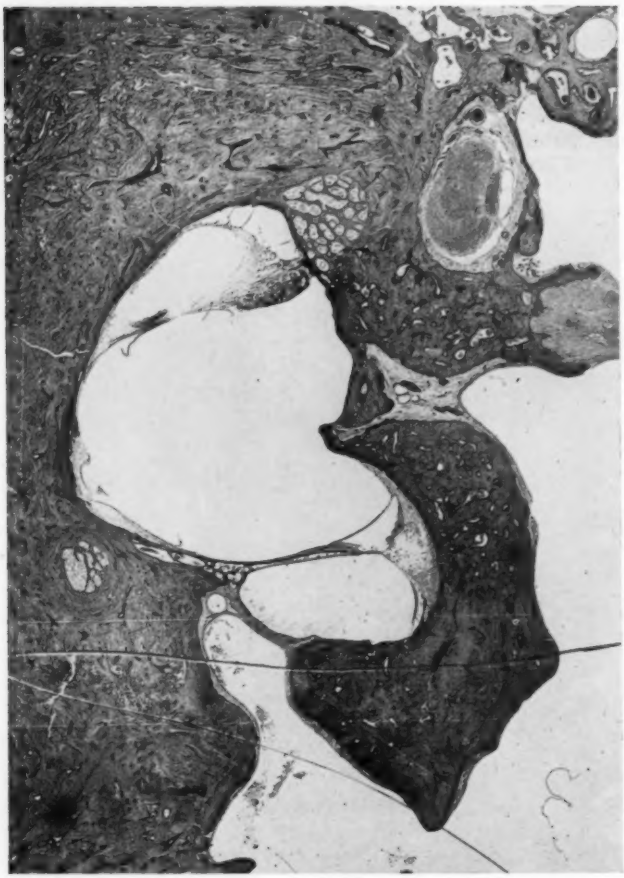

Fig. 6. Female, age 104. Photomicrograph of vertical section through the stapes. Advanced otosclerosis with total loss of hearing for air and bone conducted sound. Marked ankylosis, sclerotic focus of otosclerosis. Round window niche was patent. Profound deafness due to inner ear degeneration secondary to otosclerosis.

borders on the niche of the oval window. If you look at the stapes on the vertical section it looks quite different.

This illustration from a vertical section shows the depth of the niche down to the footplate. The view of the footplate at

operation is partly obscured by the borders of the niche, also by the fact that directly over it are the crura and the incus. The view which it is possible to get of the footplate is somewhat limited.

This next case of ankylosis is from a patient who was totally deaf at the time of death. The following two illustrations also show extensive otosclerosis. They illustrate how hopeless it might be to expect to get a good mobiliaztion in the really advanced cases. Here you see a large otosclerotic focus extending across the footplate, and to expect to mobilize it would be hopeless. The next three illustrations also show advanced otosclerosis at the footplate and are cases in which any attempt at mobilization would be hopeless.

DR. HOUSE: Thank you, Dr. Lindsay. I am sure you can visualize now some of the problems which we attempt to face when we surgically mobilize the footplate.

I should like now to call on the next participant of our symposium, Dr. Victor Goodhill. Now the remaining members of our symposium will speak more on the problems pertaining to indications, what they themselves tell patients pertaining to mobilization surgery, what they are doing in the way of tricks and techniques, following which we will go into the summary of the results.

DR. VICTOR GOODHILL: Stapes mobilization is neither a standard operation nor is it applied to a standard disease. Stapes mobilization is used in the surgical approach to relieve stapes ankylosis in what we call for convenience, "clinical otosclerosis." This stapes ankylosis may be due to histological otosclerosis, about which we know too little, or to other bone diseases, some known, some still unknown. Dr. Lindsay has pointed this out clearly.

In conductive deafness of presumably otosclerotic etiology, exploratory tympanotomy is now indicated. We may find other lesions, such as fibrotic periostitis, ossicular dislocations, ossicular or fenestral anomalies, etc. If such exploration reveals

footplate ankylosis, the stapes mobilization approach is physiologically logical.

The objectives of stapes mobilization in such cases are dual: *1.* Restoration of near normal mobility to foot plate; *2.* Maintenance of integrity of the middle ear mechanism (which contributes approximately 26 db of impedance matching normally).

The indications require new and broader audiologic conceptions. Basically, the surgical approach is indicated if pre-operative bone conduction measurements indicate the possibility of restoration of air conduction thresholds to the 30 db average level. Sometimes it is possible to hope for this level when bone conduction is lower than 30 db, *i.e.*, 35 db or 40 db, or even 45 db. Bone conduction, in my opinion, is usually an indicator of *cochlear function*, which is at least at the same level, and sometimes even better than the bone conduction level; but there is another indication for mobilization, and that is in certain types of profound mixed deafness, presumably of basic otosclerotic etiology where the bone conduction would be too low to hope for serviceable restoration of hearing. In such cases (b. c. levels of 45 to 55 db) it is possible to hope for improvement to a level where hearing aid performance can be greatly enhanced by improved discrimination, diminished feedback, and elimination of recruitment, which is so commonly found in high level deafness.

The patient is told that the procedure may or may not be successful; that it may be successful in one ear and not in the other; in both, or in neither. If, by the usual criteria, the patient is also a candidate for fenestration surgery, he is told that fenestration remains as a secondary possibility in case of failure or persistent reankylosis. Since the audiologic indications of this approach are broader, obviously *not all* of these patients are going to be fenestration candidates in the event of failure.

Now some remarks about technique—Based upon the two principles enunciated, footplate motion must be obtained, and normal middle ear function must be maintained.

This is an approach requiring multiple techniques because of multiple-pathologic states. One cannot operate on an "all or none" law. Application of force must be guided by quantitative techniques, obtained only from surgical audiometry.

In this approach one must be especially aware of the surgical rule of *non nocere* in planning surgical steps. This is decidedly not simple surgery. I will not go into the details of my technique, which has been described in several publications. I would like only to stress some aspects. Local anesthesia and the trans-canal approach are used. The incision is a generous one for several good reasons. Adequate removal of bone from postero-superior quadrant for good exposure is an obvious necessity in many cases. The use of the microscope for examination of details is extremely valuable, but in many situations it has been found that the microscope interposes a mechanical obstacle to the delicate manipulations necessary in this surgery. There are many delicate maneuvers needed in the various procedures and steps of this approach. The microscope unfortunately seems to interpose a solid object which does not allow for complete flexibility or fluidity of motion.

The actual surgical approach consists of a progression of steps, depending upon the gross pathological findings.

1. If palpation reveals a stable incudostapedial joint and rigid crura, then one or two procedures may be effective in obtaining lysis of the ankylosis.

a. The trans-incudal digital approach uses a small needle-shaped probe anchored within the periosteum of the lenticular process of the incus. Digital vibrato force is then applied. If lysis cannot be obtained, then this step is followed by

b. The use of a small electrically controlled micro-vibrator placed in the same trans-incudal position.

2. If we find on palpation that the incudo-stapedial joint is loose, but the crura are still rigid, the application of force is transferred to the capitulum of the stapes. The lenticular process is moved very slightly away from its capitular attachment, so that

a. The needle probe may be inserted into the capitular surface of the stapes and force applied by digital techniques, or

b. The micro-vibrator may be used if digital techniques alone are inadequate.

3. If palpation reveals atrophic or non-rigid crura, then the only approach possible is a direct footplate approach. I believe Dr. Lindsay's slides pointed this out most eloquently. In many of these cases the footplate is a deformed structure, and the crura are delicate, slight, senile bony struts, which are very easily fractured. In these cases it seems desirable to go to the footplate. Techniques used on the footplates today are extremely varied and highly experimental. One may use a probe, an electric or pneumatic hammer, the new intertia vibrator, a chisel, or any other instrument. They are all, at present, in preliminary experimental phases. I would like to point out that simple puncture of the footplate will frequently produce a spectacular improvement in hearing on the operating table, which will be a very encouraging step temporarily; however, in many cases this spectacular improvement *(step 3)* will disappear completely or partially when the drum is closed (*step 4* of surgical audiometry). The improvement in hearing one would expect with closure of the drum does not occur, but there is actually a drop in hearing. In these cases, it is my opinion that one has done nothing but a temporary puncture-fenestration of the footplate, one which in most cases is temporary and destined to immediate closure. Here we see another reason for the necessity of surgical audiometry, in that it gives us details of middle ear physiology otherwise unobtainable.

If the footplate maneuver is successful and is accompanied by physiologic continuity of the mobilized fragment with either one or both crura, one may hope for a significant gain in hearing.

Closure details are important. Meticulous removal of blood is important. Blood clots may ruin an otherwise excellent mobilization. Precise gentle canal packing is important in preventing postoperative oozing and excessive postoperative edema.

Surgical problems merit a few words. Incudostapedial dislocation is certainly not a desirable accident and should be avoided whenever possible. Whenever it occurs the incus should be carefully repositioned upon the capitulum. The same philosophy applies to crural injuries, whether they be complete fractures or green stick fractures. They should be avoided. If they occur, the fragments should be repositioned wherever possible. Bleeding should be controlled by electrocoagulation and packing, because, as I mentioned before, it may be a significant postoperative problem.

Vertigo is usually not a serious problem in this surgery. There is frequent inconsistency between the occurrence of vertigo on the operating table and what happens to the hearing. Usually there may be momentary vertigo at the time of successful mobilization, but it is possible to have no vertigo with marked improvement in hearing. It is possible to have a great deal of vertigo with no improvement in hearing.

Perforations are not infrequent. They usually are small, slight tears. In my practice I always close them with a small thin free skin graft, and they are invariably healed at the end of a week.

Antibiotic therapy is of course advisable to prevent otitis media and labyrinthitis. We use the mycin drugs.

The packing is removed on the sixth or seventh day. Occasionally tubal inflation may be necessary three or four weeks postoperatively.

I feel strongly that surgical audiometry is a necessity for this surgical approach. I do not have time to go into details, but some type of relative measurement is necessary in guidance. For this purpose we have been using the surgical audiometric *nomograph*, which has been recently described as a guide to stapedolysis surgery.

I should like to point out that reankyloses do occur, and the percentage is difficult to estimate at this early stage. Reankyloses may occur at any stage of the postoperative period; they may occur very early, within several weeks, several months, or even a year later. It seems that they are more common fol-

lowing footplate techniques than when the approach is through the incus or through the stapedial capitulum.

Can reankylosis cases be re-operated? Yes, they can, and in some cases they may be more successful in a secondary procedure than in the first procedure.

As far as candidate selection criteria are concerned, I must conclude at the present that any otosclerotic patient with a marked conductive deficit, with reasonably decent bone conduction, is a suitable candidate. Preoperative bone conduction, air conduction, air-bone gap, age, and other factors have been studied. I have been unable to come to any conclusions regarding these factors as significant guides to candidate selection.

In summary, in clinical otosclerosis, as we conceive of it today, stapes mobilization is a useful procedure. It is a precise micro-surgical approach to the stapedial vestibular joint. It should be a tool in the hands of the otologic surgeon who is trained and experienced in all phases of temporal bone surgery including fenestration. It is extremely early; in its present status there are no final well defined standardized techniques.

In all of our modifications and improvements, however, two things must be remembered. We are trying to accomplish:

1. Restoration of motion to the ankylosed footplate, and

2. Maintenance of the integrity of the middle ear mechanism.

DR. HOUSE: Thank you, Dr. Goodhill. I will ask Dr. George Shambaugh to present his portion of this symposium.

DR. SHAMBAUGH (showing of movie): This movie depicts the current technique which Dr. Derlacki and I are using. I emphasize, it is our current technique because this is an operation which is very much in the developmental stage. We are constantly changing our technique, and I am sure as time goes on everyone else will be changing his also.

Three things are emphasized in this technique: one is direct visualization of the footplate; second, the use of the operating

microscope, which we think is essential for the best results; and the third is the use of pressure directly inward toward the vestibule as our principal attack on attempting to mobilize the stapes. This technique, which we are showing, is a combination of Dr. Rosen's, Dr. Kos', Dr. Goodhill's and Dr. House's, with a few ideas which Dr. Derlacki and I have added.

We tell our patient with otosclerosis who is ideally suited for fenestration that he has a choice of a new experimental and very uncertain procedure called stapes mobilization, or a very well established, dependable and relatively certain procedure of fenestration. We then give him, as well as we can, the advantages and disadvantages of these two procedures, and we do it in writing so that he may take home the information and at his leisure consider it and make up his mind as to what he would like to have done. The advantages of stapes mobilization, we tell him are, first of all, its simplicity as far as he is concerned, with only three days away from work as compared to three weeks with fenestration in the average case. Usually there is very little vertigo compared to fenestration. The hearing improvement, if successful, is comparable to that obtained by fenestration and occasionally, but only occasionally, exceeds that obtainable by fenestration, and finally, and we think most important, there is no postoperative cavity requiring care the rest of that patient's life.

The disadvantages of stapes mobilization, we tell him, are first of all, the complete unpredictability and uncertainty of the result. We have no way of knowing until we get into the middle ear as to what type ankylosis he has, and whether or not it will be suitable for mobilization. Second, as yet we know nothing of the permanence of the result of this procedure. Third, the chances of failure are at least as great as the chances of success, so that in all probability this patient will have to come back for subsequent surgery. We are very conservative in our promises to these patients. We emphasize that this is a preliminary surgical procedure only, and he should consider it as such. If he is very fortunate it will be successful, and he will not need another operation; but he should be prepared to return for the fenestration operation six months

later. This is extremely important, because psychologically these patients tend not to try a second operation if the first operation has failed.

We remove quite a bit of the bony rim in the average case, 3 or 4 mm. in many instances, in order to get an excellent view of the footplate from above. Nearly always, in spite of the narrowness of the oval window niche, we can obtain a view of at least half of the foctplate. We sacrifice the chorda tympani very often and explain to the patient ahead of time, "You must expect the sense of taste to be deranged for a few months."

The footplate as seen through the operating microscope has a bluish color; when normal, white and interlaced with vessels when replaced by otosclerotic bone. We use magnification of 16 times for most of our manipulation. We believe audiometric control of the procedure is extremely important. Our first test is made with the tympanic membrane replaced after elevation, when we have a traumatized, relaxed membrane closing the middle ear cavity. This test is our base, to which we compare any improvements obtained by our manipulation.

Our first attempt at mobilization is through the lenticular process of the incus, using a blunt ended mobilizer that we call the "Derlacki mobilizer" rather than a sharp needle. The needle frequently will split the incus or head of the stapes. Our chief direction of force, using intermittent pressure, is directly inward. That is the direction in which the crura are constructed by nature to take the greatest force without fracture, and we have had our greatest success in obtaining mobility by this maneuver. If the lenticular process fractures we then transfer pressure to the head of the stapes, watching for movement of the footplate itself. In some cases we can see a line of fracture in the footplate, often with escape of perilymph.

I would estimate that in about half the cases that we are able to mobilize we do so working through the incus, and in the remainder through the head of the stapes. Rarely do we go directly to the footplate. We are still very hesitant about this, because of the possibility of labyrinthine damage. It should

be remembered that the chance of making the hearing worse by mobilization is three times greater than by fenestration.

A good many of the cases that are audiometrically improved on the table will drop down within the next month. After one month it is less common to have the hearing decline, but gradual loss of the improvement due to refixation of the stapes can occur many months after an initially successful result.

DR. HOUSE: Thank you very much, Dr. Shambaugh. I am sure that this emphasizes again the value of visual education when you are attempting to describe techniques; indeed a very beautiful film.

I will now call on Dr. Kos to give his thoughts on stapes mobilization.

DR. C. M. KOS: Few surgical procedures of comparatively recent history have aroused such professional imagination and intense interest as the current employment of stapes mobilization. Judging from the frequency with which this procedure is being used and the numbers of those who are investigating its value, it should not be long before current uncertainty and skepticism may be swept aside or confirmed.

For the present, patients who accept the recommendation of stapes mobilization should be thoroughly apprised of the uncertainty of receiving hearing improvement. This uncertainty cannot be couched in terms which underestimate the incidence of failure. There is nothing about the otoscopic examination or the audiometric findings which permits me the latitude of predicting a given result.

It seems reasonable to inform the patient that there is some chance of recovering practical and serviceable hearing, and that the likelihood of residual damage or injury to the ear structurally or functionally is a very remote one.

While they are rare, the risks and complications seem to be directly proportional to the ability, training and experience of the surgeon. He should be qualified and prepared to give definitive otological treatment, and to accept the responsibility

of managing any problem that may arise in connection with his efforts. The most common risk is in increasing the hearing loss due to fracture of the crura, excessive trauma to the stapes, or postoperative adhesions. This may add 10 to 15 db to the preoperative impairment and consequently increase the intensity of the tinnitus.

Other complications may include tympanic perforations, otitis media and labyrinthitis. Appropriate caution, a meticulous technique and protective antibacterial therapy should reduce these to an extremely low incidence.

Facial paralysis is possible, but it can be avoided if carelessness and incompetence can be eliminated. Temporary paresis or paralysis may result from an intent to infiltrate the anesthetic agent too widely and too deeply.

The eardrum may become undesirably flaccid because of an imperfect replacement of the epithelial cuff or because of subepithelial bleeding.

Postoperative bleeding may be annoying but not of a serious consequence.

Injury to the chorda tympani nerve may cause the complaint of perverted taste in a few instances.

Should the mobilization procedure prove ineffective, the patient should know at the outset whether the fenestration operation may be the next step required to achieve hearing improvement.

In the event satisfactory hearing improvement results from stapes mobilization and then regresses, the procedure may be repeated, and so far as is currently known, may be repeated indefinitely at six to 12 months' intervals.

A variety of techniques may be required to bring about release of the ankylosed footplate. Sometimes the pulsating pressure applied to the neck of the stapes, as described by Rosen, will suffice. In many instances a special pick inserted into the head of the stapes through the lenticulo-capitular capsule has given excellent results.

This approach (slide) is personally preferred for the firm leverage it exerts on the footplate through the crura. Upon mobilization the epithelial cuff is replaced, and a thin strip or a compressed strip of gel foam is placed over the incision; I do not use packing. The patient is in the hospital one day, arriving in the hospital the night before the operation is done, and he is discharged at four o'clock that afternoon.

In other instances mobility may be obtained by exerting pressures on the lenticular process, such as Dr. Shambaugh and Dr. Goodhill described. It may be necessary to apply the picks in a prying manner to the edges of the footplate in order to secure adequate mobilization. In others, a mechanical device such as that used by Dr. House may be directed at the footplate so as to fracture or even pulverize the structure.

It is apparent, from these few technical preferences, that the search continues for effective and safe techniques which may increase both the incidence and durability of successful results. It is rather obvious at this point that the demonstration of some success has stimulated an inquisitive drive and inspired a general curiosity which may lead to better solutions; but this is not the stage in the development of this procedure for unlimited enthusiasm.

DR. HOUSE: Thank you very much, Dr. Kos.

Dr. Ned Fowler will now close the participants' portion of this program, except for their responses in discussion.

DR. EDMUND P. FOWLER, JR.: I regret that the other panelists did not go into the indications for mobilization of the stapes more clearly since this was part of Dr. House's charge to us. We have discussed the indications, however, and I think that most of us seem to agree that mobilization procedures are indicated on any case which is suitable for fenestration; they also can be done on patients who are so advanced in years that fenestration is unwise. Mobilization procedures can also be done on patients who do not wish a major surgical procedure, or the inconvenience of a radical mastoid cavity, and also on patients where the bone conduction is down so much

that a successful fenestration operation will not bring the hearing to a practical level. Closing the air-bone gap in severe deafness will often just bring the hearing to the 30 db level or will occasionally permit the wearing of a hearing aid with comfort.

Dr. House admonished us to tell exactly what we say to each patient. I tell each patient that two out of three cases get a bad result; that *he* is, therefore, likely to get a bad result. Now the reason I say "two out of three" is because I really don't know how many bad results there are going to be in the future, although I have some theories on the matter which I shall relate later. I try to emphasize that two patients out of three get a bad result, because I wish nobody to sue me or come in with a blackjack, or complain that I have minimized anything; however, I do bring out the facts that very few cases have any complications. There are a few patients that have a slightly increased hearing loss, from the operation, especially if there has been much manipulation of the footplate; and there are a few patients who have lost their hearing completely, or almost completely. The statistics on this phase will be brought out later by Dr. House. Since the worse ear is usually operated, a slightly increased hearing loss will, as a rule, be of comparatively little consequence. I always discuss fenestration and further rehabilitation with a hearing aid with the patient, and point out that there is very little chance that the hearing will be made sufficiently worse by mobilization that a fenestration cannot be done in the future.

If the patient asks me how much discomfort there will be I usually tell him, "about as much as having a wisdom tooth out." Having a wisdom tooth out can be quite a serious procedure, as some of you know, and I think that some patients have much less trouble than others, but I believe that comparison with molar extraction is fair, from the standpoint of the patient. The standpoint of the surgeon is quite another matter, for I do not believe that mobilization procedures are simple; on the contrary, I think they are more difficult than fenestration.

At the Columbia-Presbyterian Medical Center we have made a series of observations and have developed a different tech-

nique from those described this morning. Incidentally, I work in such close collaboration with Dr. Franz Altmann and Dr. Milos Basek that I hardly know where their ideas leave off and mine begin in this discussion of our philosophies and the technique that we have developed in our laboratory. After months of observations we feel reasonably certain that mobilization of the stapes with the Rosen techniques and the modifications of them used by Goodhill and House do not break

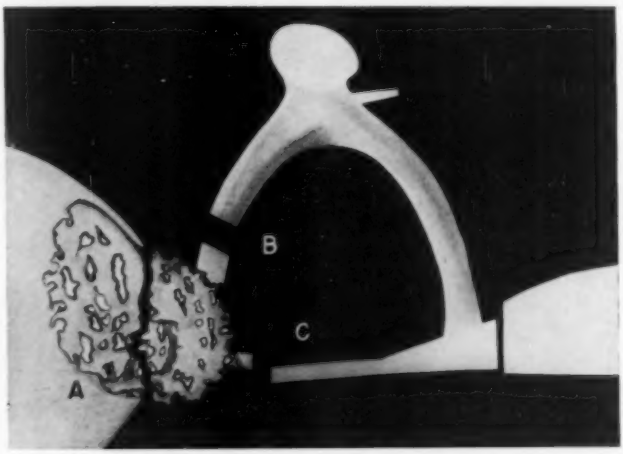

Fig. 1. Diagram of otosclerosis focus in anterior border of oval window in horizontal section. Mobilization through "A" impossible, or if accomplished would soon be followed by re-ankylosis. Anterior crurotomy "B" with footplate fracture; "C" brings about mobilization through the posterior crus.

up an ankylosed joint. We believe that mobilization is best attained by footplate fracture and deliberate severance of the anterior crus of the stapes. Our reasons for this position are as follows:

(Fig. 1 typical otosclerosis with ankylosis of the anterior part of the stapes with heavy cancellous new bone). With this type of otosclerosis I cannot see how one can possibly mobilize the stapes through the vestibulo-stapedial joint, in the manner

suggested by the writings of most authors on the subject of mobilization.

(Fig. 2.) In this kind of ankylosis where there are calcifications of the annular ligament from otosclerosis, I should think that if you shake the ankylosis loose, either with a vibrator, hammer or pick, that the patient who says "doctor, what

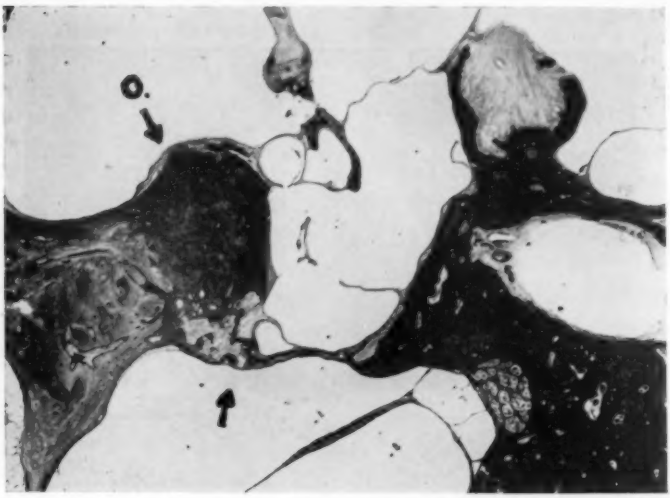

Fig. 2. Section through oval window showing ankylosis by calcification (arrow). After breakage, such calcified spicules would theoretically reform. Note excess fibrous tissue which would be unaffected by manipulation of the head or neck of the stapes.

is going to keep this thing from rehealing" has a point. This sort of calcified joint is likely to be reankylosed just as any other joint in the body, if loose calcium spicules are present.

In Fig. 3 we show a type of otosclerosis where we have extensive new bone growth which involves the entire footplate. I cannot see how anything except breaking of both crura could occur with manipulation of the head of the stapes, in such a case. (At this point I should like to say parenthetically that in histological sections we can show only one part of the curve

of each crus in longitudinal section, and, therefore, it is not quite accurate to consider that what you see under a photomicrograph is the entire thickness of the crus. As you know, each crus is hollow with the curve inward. Whether one can mobilize a massive ankylosis of the stapes or not is a great question. Cases of severe deafness having an improvement

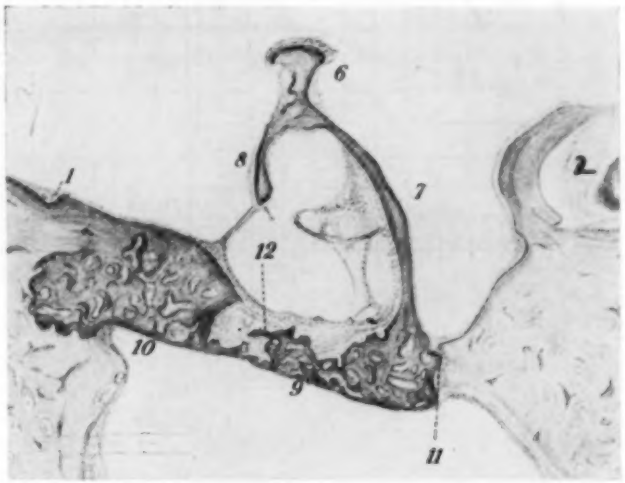

Fig. 3. Nearly horizontal section through otosclerotic stapes. With massive ankylosis of this type it is doubtful if mobilization can occur unless there are normal areas in the foottplate which can be fractured. (1) Tympani plexus. (2) Facial nerve. (6) Head of stapes. (7) Posterior crus. (8) Upper part of anterior crus. (9) Cartilage of footplate replaced by otosclerosis. (10) Ankylosed annular ligament. (11) Partially ankylosed posterior part of annular ligament. (12) Calcified spicule in region of annular ligament. (From Bruhl) (1).

have been reported. I have been successful in only one case in which I have seen new white bone growing across the entire footplate.

Dr. Altmann, Dr. Basek and I found in the laboratory that unless we used the dissecting microscope we could not see what we were doing. In the operating room we cover it with a polyethylene or Dupont Mylar sleeve which is transparent and can be well sterilized (see Fig. 8). We can see exactly what mag-

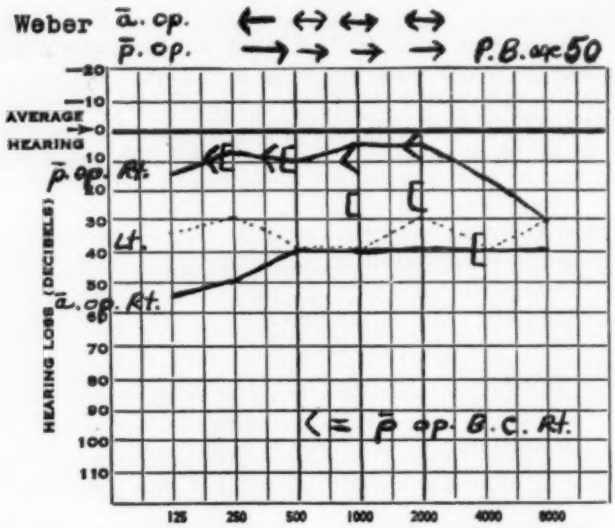

Fig. 4. Audiogram of case of anterior crurotomy, in which inadvertently the posterior crus was cracked, but not displaced. Note elimination of the "Carhart notch" and fact that posterior crus probably rehealed to give such good hearing for air conduction.

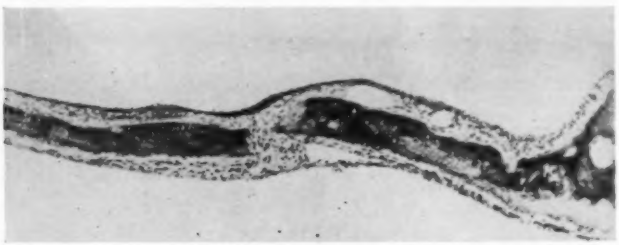

Fig. 5. Healing of fractured footplate by fibrous union. Autopsy 56 years after injury. From Hallpike (2).

nification we are using, with this type of cover, and we can also have the camera in place and manipulate the controls of it without undue difficulty. We work with 4x, 6x and sometimes 10x magnification, but we check the footplate with 16x and 25x, after what seems like a successful manipulation.

I am showing the audiogram in Fig. 5 because I am later showing a movie where the same sort of thing happened as was recorded in the operative dossier of this patient; namely, when the anterior crus was cut, it was seen that the posterior crus was also cracked. There was no displacement of the posterior crus; and I believe that it grew together again, because in the audiogram you will notice that the air conduction im-

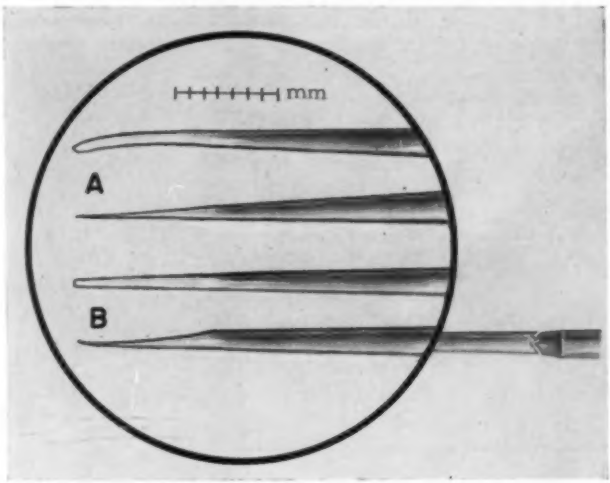

Fig. 6. (a) Saber of Basek for weakening and cutting the bone of the footplate. (b) Hand chisel of Basek for cutting across the footplate, 0.5 mm. width, fashioned from a needle; this is used when the footplate cannot be cracked with a saber. Slight pressure and a rocking movement are used.

proved considerably. Incidentally, the bone conduction postoperatively also improved. The Carhart notch is eliminated, thereby proving the theory of Carhart that a 15-20 db BC loss at 1,000 and 2,000 has something to do with inner ear impedance rather than a loss of nerve function.

Finally, as we show in Fig. 6, some of our thinking is based on an observation of Hallpike's.[2] This is similar to a case reported by Dr. Altmann[3] where he, too, shows that when the footplate is fractured it does not heal by bony union, just as

the fractured endochondral bone of the labyrinth capsule does not heal by bony union. I think that such fibrous union is what we get when we mobilize the footplate by any of the techniques used by the men participating in this Symposium. I do not think that we get any improvement of hearing unless we mobilize the footplate and fracture through its normal areas. I

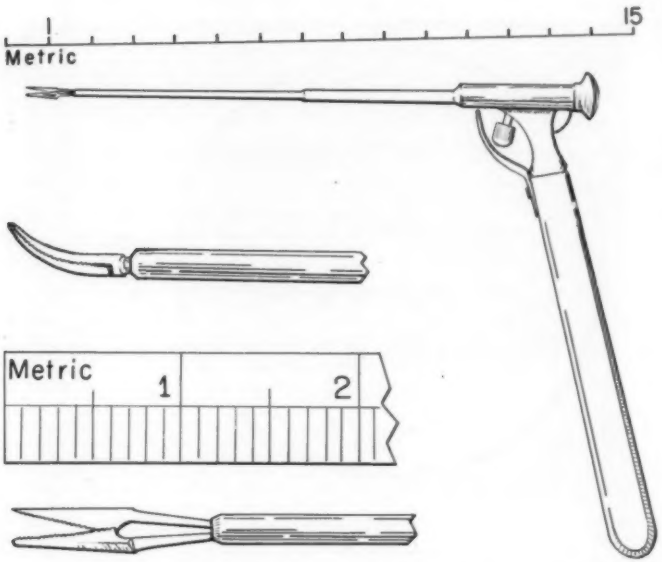

Fig. 7. Anterior crurotomy scissors with correct curve and serrated edges.

believe we are going to have a good lasting hearing in our successful cases because of this observation of Hallpike, confirmed by Altmann. I also believe that we must design our techniques to produce a fracture of the footplate and to release the anterior crus from the bony growth in the promontory anteriorly.

That this is feasible was then shown in a movie picture illustrating the following points: The material used was fresh cadaver specimens, artificially ankylosed either with adhesions

or with dental wax preparations. It showed the operation as performed by Altmann, Basek and myself as follows: *1.* Incision from above the short process of the malleus through 180 degrees; *2.* Elevation of the sleeve of skin to the edge of the annulus; *3.* Slight inadvertent elevation of the outer epithelial layer of the drum, which was not continued because of the magnification being used; *4.* Entering the Rivinian notch with a pointed needle, so as to perforate the mucous membrane lin-

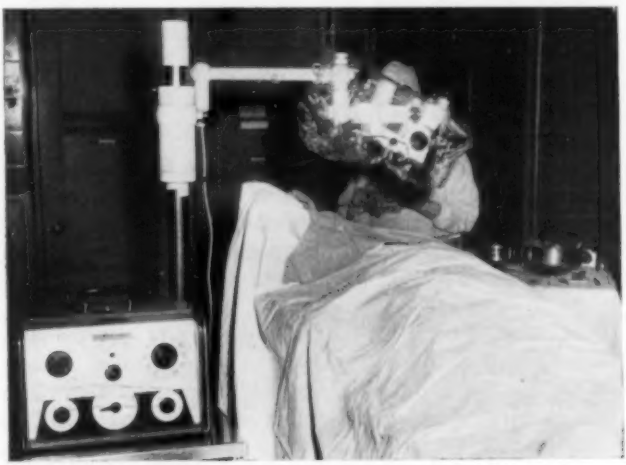

Fig. 8. Dissecting microscope (4x to 40x) with multiple movements and counterweighted focus, built in illumination, 20 cm. or 30 cm. working distance; flash and camera attached and covered by sterile plastic shield with audiometer on the left. Nurse and instrument table in background. High rod covered by drapes gives patient comfortable breathing area. Objective of microscope is somewhat lower and more tilted when in actual use.

ing of the middle ear and not dissect it away, as sometimes occurs if this maneuver is not carried out; *5.* Elevation of the drum from above downwards, by pressure on the fibrous annulus, thus lifting the drum from the bony annulus from above downwards rather than from outside in; *6.* Cutting away the bone over the chorda tympani to obtain a good view of the footplate and the anterior crus; *7.* Weakening of the footplate with the needle-like sabre of Basek (see Fig. 6); *8.* Cutting the anterior crus with special scissors (see Fig. 7) so that the

shearing action of the scissors crack the footplate in its already weakened line.

The moving picture also showed what occurred with the maneuvers of Rosen; namely, that the anterior crus and the footplate broke if the anterior crus was weaker than the posterior crus when one pushed backward on the neck of the stapes according to the classical method of Rosen. This, however, occurred in only about one-third of the cases. In the rest, both crura broke and the footplate, as a rule, stayed intact. There was some discussion of the normal movements of the stapes, also more detail concerning the anatomical considerations for the anterior crurotomy procedure. Most of this discussion can be found in the June issue of the *Archives of Otolaryngology*, 1956.

In conclusion I acknowledge grants from the Research Council of the American Otological Society and from the New York Foundation. It was these which made possible detailed investigation into the histology of stapes ankylosis and the modus operandi of mobilization procedures.

DR. HOUSE: I believe that the members of our panel have indeed presented to us a very excellent detailed review of what we are doing today in the field of mobilization surgery in this country. I am sure it points out very clearly that there are many problems yet to be surmounted. It is only through the work that you have seen as the result of this symposium, and the work that has been done by many others who are members of this organization, that we can finally evolve some of the answers to the perplexing situation.

I shall make no effort to review each gentleman's presentation; they did it so thoroughly and so beautifully.

I would like to go back a moment, however, and emphasize a few points about indications. I was glad Dr. Fowler emphasized that subject a bit because I too feel that perhaps it was not clearly explained to you gentlemen, many of whom are interested primarily in the indications for this surgery. Many of you will not do this surgery, but you will want to know when it should be done and what to tell your patients.

As far as indications are concerned, I think all of us on this panel are mutually agreed that any patient who is suitable for fenestration is likewise suitable for mobilization. I believe we are safe in saying that every member of the panel will recommend or advocate mobilization first, to be backed up by fenestration if and when it is necessary, and providing, of course, that they are suitable for fenestration. Many patients who are suitable for mobilization, are not suitable for fenestration. One, for instance, the debilitated patient; two, the patient with a unilateral hearing loss who, perhaps, we would not recommend for fenestration but would certainly recommend for mobilization; third, the individual who has a far advanced nerve type of loss, providing there is still a spread between the bone conduction curve and the air conduction curve sufficient to give that individual an improvement, even though he may have to continue with his hearing aid afterward. Nevertheless, such improvement is extremely valuable to many patients. It has been amazing to me, as I am sure it has been to other members of this panel, the difference between having a 60 db loss and a 40 db loss.

Now a word about what is told to patients regarding conservatism, caution and great care in educating them to the overall otologic problem, not with the thought that we are going to do a mobilization and that is the end. We, as otologists, must render to our patients a complete otologic service, of which mobilization is but one part.

As far as technique is concerned, you have heard what is going on in the way of technique. I am sure you will realize there are almost as many different techniques being used as there are men doing the operation. That is to be expected in this relatively early exploratory phase of this new procedure; and, perhaps like fenestration, sooner or later we will evolve a rather constant and standard procedure. You have heard each of us express the fact that it is not a simple operation and is not without possible serious complications. Likewise, it is an extremely delicate procedure, as illustrated so beautifully by our good friend, Dr. Lierle, in his presentation.

With these few comments I will now review the results of the cases forwarded to us for analysis.

In this group of cases (slide) are represented a total of 1,091 mobilization cases operated up to the time of this analysis, one month or longer prior to sending in the information. You will notice that the overall cases total 1,091 and of that number 35 per cent reached the level of 30 db or better. As you will see later, this also includes all of those cases which did not have a chance to reach the 30 db level in some instances, because of rather far advanced nerve deterioration.

We divided these cases (slide) into three main groups, the "A," "B" and "C" cases. We will classify the "A" cases as that group which had a loss by bone conduction of 10 db or less at 500, 1000 and 2000 cycles; therefore the so-called ideal case for fenestration. Of this series of slightly over 1,000 cases, 24 per cent were represented in this group, so that we had 24 per cent of this series that were ideal or "A" cases. At the end of one month the average for all the 1,091 cases which had reached the 30 db level or better was 58 per cent. The highest group was reported as 66 per cent reaching the 30 db or better level at one month. The lowest group in the series was 43 per cent.

We classify as "B" cases (slide) those having a loss of 20 db or less at 500 and 1000 cycles, and 30 db or less at 2000 cycles. This group represented 43 per cent of this series. At the end of one month 38 per cent of these 1,000 cases which fell into this category reached the 30 db level. The highest group reported 46 per cent of these cases having reached the 30 db level, the lowest group reporting 18 per cent.

The "C" cases (slide) are those which have a loss greater than 20 db at 500 and 1000 and 30 db or more at 2000 cycles. The total in this category represented 33 per cent. Those reaching the 30 db level at one month in the average were 25 per cent. The highest group reaching the 30 db level in this group was 54 per cent. That is an interesting figure, because it means that in this particular series it would seem that the bone air gap, the difference between air conduction and bone conduction, would of necessity have to be completely, or almost completely closed, to reach the 30 db level. I would imagine that this is the result of what statistics can do on occa-

sion. The lowest group in this category, 5 per cent, reached the 30 db level in the "C" cases.

Now let us break this down a little further (slide) and see what happened to each one of these operators as a group when we compared their first 25 cases with their last 25 cases. We see that 10 per cent of their first 25 cases closed the bone air gap completely, that is the spread between air conduction and bone conduction. In the last 25, 17 per cent closed their bone air gap completely. How many closed within 10 db of the gap? 13 per cent in the first 25, 15 per cent in the last 25. How many closed within 11 to 20 db of their bone conduction curve? 13 per cent in the first 25 cases, done, in the last 27 per cent; therefore the total, you see, in the first 25 cases of the men in this symposium, 36 per cent did not reach the 30 db level but fell within these three categories, not necessarily being within the 30 db level. The last 25, 59 per cent, fell into these three categories. I think this is extremely significant, because it points out the value of experience in this work, the necessity of the training that must be had, the delicacy of touch, etc., that can be acquired only by working in fixed stapes and footplates.

Now let us see what happened to closure of the bony area (slide). It is interesting to note that 46 per cent of the total cases, therefore, closed the air bone gap within 20 db of the bone conduction curve, regardless of what the bone conduction curve showed.

The average closing to the bone conduction curve completely (slide) was 11 per cent, the highest group 21 per cent; the lowest group 6 per cent; those closing within 10 db of bone conduction averaged 16 per cent; the highest group 37 per cent, the lowest 9 per cent, and within 11 to 20 db of bone conduction the average was 19 per cent; 21, the highest and 10 the lowest.

Now let us talk about our failures (slide); 15 per cent of our cases in this symposium were 0 to 10 db worse by air conduction. That means that if they were even 1 db worse by averages they fell into this category, which obviously is well within audiometric allowances. If we allow 10 per cent

averages for the three speech frequencies as being audiometrically questionable, we would say, then, that 3 per cent of our cases were worse between 11 and 20 db by air conduction; so 3 per cent are worse by more than 10 db and less than 20 db, and that 2 per cent were more than 20 db below the preoperative level. If we look at the bone curves, it is rather interesting to note that 4 per cent of the cases operated had a lessening of the bone conduction ability following surgery. They were down 25 db, or less in 4 per cent. Most of those obviously were done relatively early, but this is an interesting and important figure: .2 per cent of the cases were down more than 25 db by bone conduction, thereby indicating apparently a damageed inner ear mechanism.

What about surgical complications (slide)? You heard the chorda tympani problem mentioned by Dr. Shambaugh and others, so we will not include that. We will simply say permanent perforations occurred in .7 per cent. Of the series, continued post-operative infection occurred in .2 per cent; persistent vertigo of an annoying degree occurred in .7 per cent. Facial paralysis, which was temporary, occurred in .3 per cent, probably from infiltration, as mentioned; therefore, the total complications of any practical degree in this case were actually 1.9 per cent. Just a little less than 2 per cent had any type of serious complications actually, except for the two patients with labyrinthine damage. I think that this speaks very well for the fact that serious complications in the hands of those experienced in this work seemed to be relatively few.

By this symposium we have attempted to bring you up to date on our thoughts and views pertaining to mobilization surgery.

DR. HOUSE: I will ask Dr. Rosen to proceed.

DR. SAMUEL ROSEN: It is extraordinary that since my work was first presented at the Triological last year in Hollywood, Fla., some of the most distinguished otologists in this country have reported here their results on hundreds of stapes mobilizations, and I am very pleased that their results tally so closely with my own.

The first patient, a chemical engineer, whose stapes was mobilized in April, 1952, attained normal hearing three weeks after operation and has maintained it ever since.

As for the duration of hearing improvement, out of approximately 1100 stapes mobilizations, all who improved 15 db or more have maintained this improvement for periods up to four years, except for 20 cases which did not fall below their preoperative levels.

I heartily agree with everything that the panelists have said. The presentation of the history of this operation by Dr. Meltzer was excellent. He rather feels, as I know I would if I had always lived in Boston, that that city was really the birthplace of mobilization in this country.

Dr. Lindsay's presentation merely emphasizes what I have felt from the beginning, that most of the time whatever was happening to the footplate during mobilization, I could not see; therefore, while some results turned out good and some did not, I really did not know what I was doing. In my opinion the first real attempt toward solving this particular problem as to what happens at the footplate when we do something at the neck is the way Dr. Ned Fowler is tackling this problem. He makes an assumption which has sense. He says that every time Rosen puts a mobilizer on the neck and successfully mobilizes the stapes so that the hearing improves, he believes that the anterior crus and the footplate are fractured, and he is going to study this problem to see how often this does occur. The fact that it occurs once merely shows that whatever happens at the neck can result in the kind of structural change described by Fowler. Now we have to find out to what degree and how often this really does occur.

Thus far I must say that I paid very little attention to this situation, because it never occurred to me until I met Dr. Fowler and Dr. Altmann a few months ago in Istanbul, where he first presented this idea; at least it was new to me. Ever since then I have in every case tried to observe as carefully as I could, with and without the microscope, to see whether Fowler's idea is correct. I did come across a patient a short time later in whom I could definitely see that I had fractured

the anterior crus close to the footplate, but because this patient's hearing did not improve on the table, I assumed that I did not fracture the footplate. I then manipulated the footplate, as I will demonstrate in just a moment, following which the hearing did improve. Maybe I really did an "incomplete Fowler."

In mobilization the variations in the structure of the stapes makes a lot of difference. Anyone who has examined several hundred stapes taken out of cadavers will see the marked changes from one to the other; very frequently from one to the other removed from the same cadaver. I must say, for my own comfort, that when I feel the neck of a stapes, as I told Dr. Day yesterday, I prefer it to be shaped something like his long neck since I am more successful in mobilizing such a stapes than when a stapes has the short neck of a Stewart Nash.

There is no way that I know, as Dr. Kos so correctly said, of predicting whether you are going to be successful in any given case. I have had so many patients in whom I have made a secret prediction that I would or would not succeed, and I can tell you that my predictability is way off. Very frequently I have been unable to mobilize the stapes, where the history of deafness is not more than five years, and I have been able in many cases to mobilize the stapes where the history of deafness is 25 or 30 years. I don't know of any audiological test at present that gives us the key to an accurate prediction.

I think Dr. Goodhill's point about exploratory tympanotomy is a good one. There are times when we are quite uncertain what we will find in the middle ear in conditions other than otosclerosis, and since the lifting up of the drum is such a simple procedure as far as its effect on the patient is concerned, I do not hesitate, though it does not occur very often, to tell the patient, "I do not know what is going on in your middle ear; I can only guess, but I would like to look in there, as a surgeon does an exploratory operation on the abdomen. I may find something which can be helped, but even if I do not find it I do not believe the procedure will hurt you."

Dr. Goodhill has spoken frequently of "incudostapedial lysis." I think we must face the fact that no matter what one calls the operation, if you do not mobilize the footplate you do not get improved hearing. After all, a "Rosen" by any other name smells like a "rose" just the same.

As for Dr. Shambaugh's presentation, his movie was extremely beautiful. I am in the process now of having a film made with Dr. Kobrak at the Otological Laboratory at Wayne University. I have been there three or four times. We have done part of it on the cadaver and part on the living subject. It is very difficult to get your head or fingers out of the way and still see what you are doing. We had to have special instruments made to meet this problem so that I was very clumsy in doing the operation with these new instruments. It is just difficult to make a good movie, but I hope we shall be successful soon.

I think Dr. Shambaugh is correct when he said that we should not have unlimited enthusiasm. I do not know how much is unlimited, but I will bet you that my enthusiasm is greater than his.

As to the operation that I described, I am sure it is not the final operation by any means. I see and hear about modifications that are being made all the time, and I often wonder how stupid I was not to have thought of the things that other fellows are doing with success; but it is going to be a long time, in my opinion, before we can use the distillate of the wisdom of all the various techniques now being tried. I am extremely hopeful.

This (slide) is as I have found it in about 3000 specimens, about half human and half cadaver; about all you see when you first lift up the drum. In 85 per cent of the cases you cannot see more than this much of the incudostapedial joint, and, therefore, I do not believe that this operation can be comfortably and precisely done until you really get a good exposure, as shown in the next slide.

The difference between trying to do a mobilization with the slide just removed as compared to this one (slide) is as though

one were trying to do a tonsillectomy in a child with its mouth half open. With this exposure I feel comfortable. I can see the structures. I can see the relationship of the structures to other structures, and one thing that I believe is very important in this operation is for one to be as relaxed all over as possible. If you do the operation sitting down you should be leaning on the patient, with (they don't seem to object to it) your arm on the patient. You should have a footstool under your feet. You

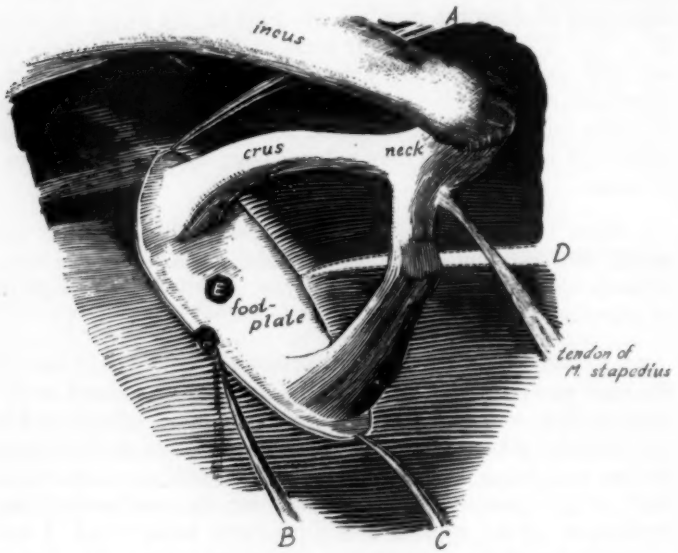

Fig. 1. (E) indicates the site of the fenestra ovalis through the body of the footplate.

should not go ahead with the mobilization when your feet are tense. If you are tense elsewhere, and you think you are relaxed in the muscles directly concerned with mobilization, I do believe that one is apt not to do it so well as if one is relaxed all over. There are times during the operation when I find myself becoming tense and when I do I just come out, put the instrument down until I relax the tensions. Most people think I am looking for another instrument. I am just

waiting for my blood pressure and pulse to go down a bit, then I pick up the instrument and try to start in again where I left off.

This (slide) brings up a very important aspect in the development of stapes mobilization. There is a good percentage of patients who, when you try mobilization at the neck, just

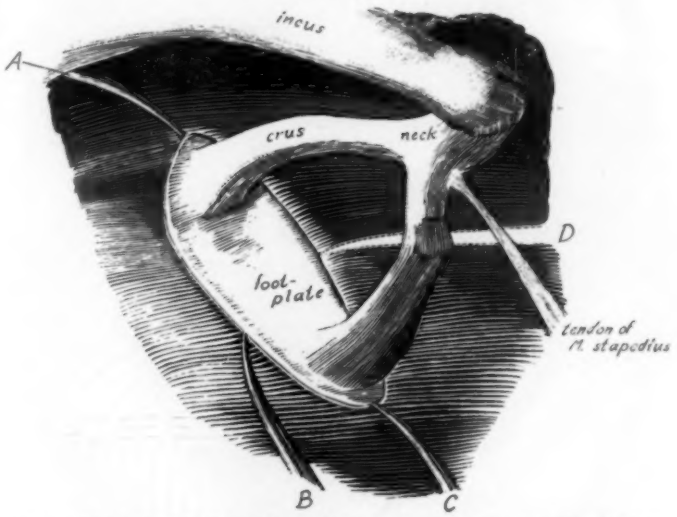

Fig. 2. "A" and "B" show the pointed explorer used anteriorly and inferiorly to mobilize the footplate. Occasionally the explorer is used at the posterior edge of the footplate "C" and rarely at the anterior edge "D."

will not mobilize. You will either quit because the crura are so thick that nothing will happen, the patient's hearing will not improve, or as more often happens one or both crura are fractured. In the early days when I felt that I was licked at this point I quit, but as time went along I decided to try very gingerly to introduce an exploratory needle between the bony ridge of the oval window and periphery of the footplate itself for a distance not greater than the thickness of the stapedial footplate, to pry the footplate loose. To my amazement I could sometimes see that as I introduced the instrument here and

just tried to move it or pry it a little, I could move it. I must say that when I first started doing this, my heart was in my mouth every time I tried it. This feeling still persists, although to lesser extent; however, I do recommend that in cases where the attempt to mobilize at the neck fails for one reason or another, we should not abandon the mobilization at that point. I might add that in some of the patients in whom I was

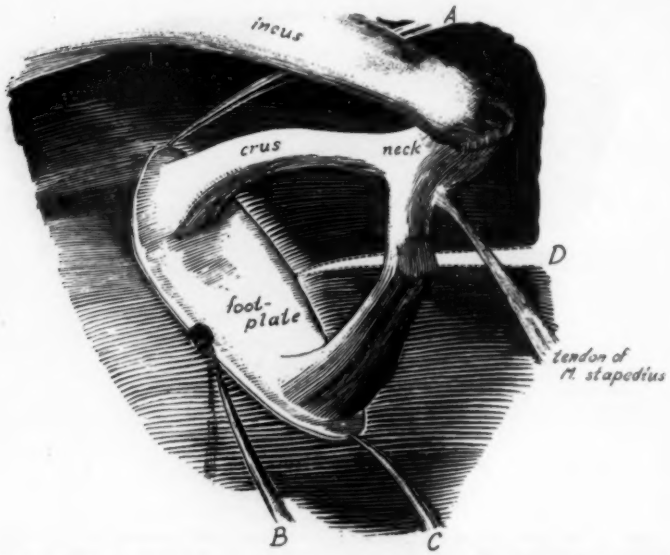

Fig. 3. Fenestra ovalis at the inferior margin of the footplate created by penetrating the explorer (B) for ½ mm. into the vestibule leaving a circular opening about half the size of the head of a pin, after attempts to mobilize the footplate at A, C, and D failed.

able to mobilize the footplate itself successfully the hearing improved to levels as high as those in whom I had successfully mobilized at the neck, even though in some of these cases I could see that the crura were completely fractured. I do not quite understand this; but I know that it has happened, and I just mention it for your information.

In this picture (slide) I have had a few patients in whom I could not move the footplate at any point. I decided that I

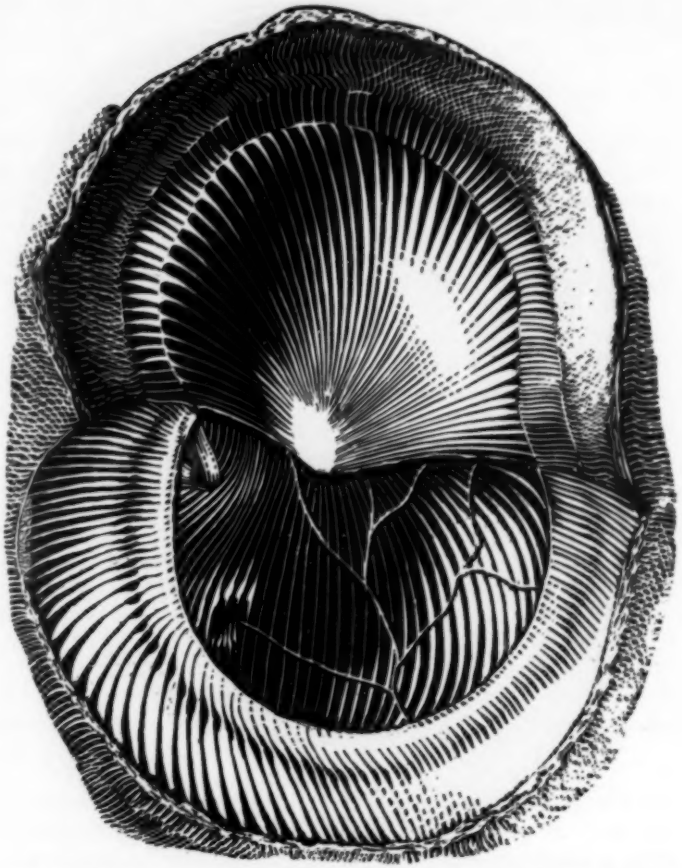

Fig. 4. When drum and skin are reflected upward, in over 85 per cent of the cases more or less of the incudo-stapedial joint is seen. This is, however, an inadequate view of the stapes that does not allow safe manipulation.

would try to make an opening into the vestibule which would include a small portion into the footplate itself, and again this was done both in the presence of crura which could not be mobilized at all and also crura which had already been fractured. In these patients—and this could really be called a

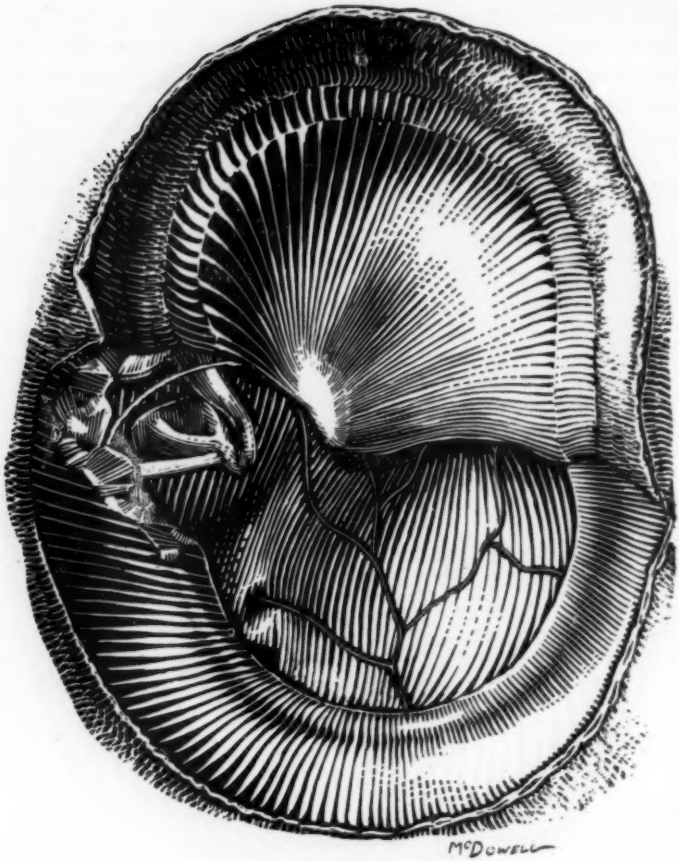

Fig. 5. After 2-3 mm. of the very edge of the posterior bony canal just external to the incus and stapes is removed, a full view of the long process of the incus, the incudo-stapedial junction, the head, neck of the stapes and the entire length of the stapedial tendon, etc., is obtained. This exposure is absolutely necessary for stapes mobilization.

fenestration of the oval window or vestibulotomy—the hearing improved to extremely high levels. I suppose that one could explain this in the absence of the ossicular chainn, by the fact that somehow the organ of Corti is stimulated, and I sup-

pose the organ of Corti does not give a hoot how it is stimulated so long as it receives stimulation.

This (slide) demonstrates some of the achievements with this operation at the neck or at the footplate itself. We have had normal hearing, and almost everyone who is doing mobilization has also achieved normal hearing. Some have had normal hearing restored in both ears. There are some patients in whom the bone conduction will not permit normal hearing, but you can still close the gap and they obtain excellent hearing, even though the bone conduction is not normal.

Restoration of useful binaural hearing is one aspect of this audiological relationship to which we do not pay too much attention. It is quite amazing the difference there is between binaural hearing and monaural hearing. You can test this for yourselves by placing your finger in one ear canal and see what it sounds like. After you have held it there for a minute see what it sounds like when you hear in both ears. You find that the difference is enormous. If the patient has excellent hearing in one ear and relatively poor hearing in the other ear, to mobilize the second ear in order to achieve binaural hearing I believe is a worthy goal.

The fourth step is to remove the stapedial component where there is a marked mixture with nerve deafness. The fifth is to restore enough hearing to allow the successful use of a hearing aid in extreme cases with deafness.

I also had a movie, but I think you get the point that I am trying to make. The purpose of this is merely to show the importance of getting the proper exposure; without a wide exposure it is extremely difficult if not impossible to do this operation. Here (film) the exposure shows the incus, the stapes, the stapedial tendon. This was done on a patient operated upon in Dr. Croushore's service at the Receiving Hospital in Detroit. The most important things to see are the footplate, the incus, the incudostapedial joint. My plea in all this surgery, no matter what technique is employed, is to make the exposure ample by removing enough of the external auditory canal edge.

Now a word or two about the revisions. I have done 96 revisions in patients who had no improvement after the initial operation; 25 per cent of those operated a second time reached a level of 30 db or better, and 40 per cent showed improvement though they did not reach the 30 db level.

Recently I operated upon a series of 77 cases in which the footplate could not be moved at all, or in which the crura were fractured. Previously, as I said, I abandoned these patients because I knew of nothing more to do; however, since I have been employing the footplate technique, not only have I revised those patients on whom I previously failed, but also in whom at the initial operation on these 77 cases I was unsuccessful in mobilization and which would have been abandoned, I went immediately to the footplate at the initial operation. 34 per cent of these patients showed improvement where they reached 30 db or better, and 54 per cent showed improvement in hearing but did not reach the 30 db level. These patients previously would have been failures, and a good percentage of them now can be improved.

I have estimated that approximately 5000 stapes mobilizations have been done in this country up to the present time. I have been all over Europe and the Middle East teaching this operation, and I believe that about 2000 of these operations have been done abroad.

It was Stewart Nash who made it possible for me to present this work in the first place over a year ago, so in the end, it is really Dr. Nash who is responsible for having brought these thousands, and I hope tens of thousands, out of a lonely world of silence into the world of hearing.

I am very grateful to Dr. Joseph Goldman, the chief of my service at Mount Sinai Hospital. He is an excellent scientist, a very shy fellow, but he has been right behind me on this work from the very beginning and encouraged me a great deal. I also thank Dr. Moe Bergman in charge of the audiology who worked very hard to keep it on the spot.

DR. BARRY J. ANSON: Emphasis on three structural features of the stapes is a warranted addendum to our previous pre-

sentation: the degree to which the ossicle has been reduced in bulk during the fetal period; the unusual weakness of the basal extremity of each crus; and (so far as known) the inability of the stapes to heal in an area of fracture.

Were there time, the discussion could be extended to include a review of the process of internal "remodeling" which the incus undergoes throughout the adult life span, and to a degree which varies with the individual. These changes, while different from those which take place in the development of the stapes, have a similarly weakening effect.

Both processes were described in a paper read at the meeting of the American Otological Society in Boston in 1954.

DR. HOUSE: I thank you for your contribution to the anatomy of this area. Since Dr. Rosen mentioned the experiences he is having with permanency over a period of time with his results, we should also make a statement about permanency in our group, although no reported cases in our series exceeded six months. We limited it to six months after surgery, and that hurts. To begin with it is interestting to note that 2 per cent of the cases that improved at the time of surgery and improved subsequently for a week or two, reccded to the preoperative level within the first month. Beyond that, little occurred in recession of hearing loss until the fourth month, when 2 per cent closed and returned to their preoperative level, only 9.100 of 1 per cent, and 9.100 of 1 per cent the second month, that is,in the fifth and sixth month of each six months, 9.100 of 1 per cent closed in each month, so that the percentage, as near as we can analyze the trend at the moment at least, is that most of them are going to close up within the first month. If they bridge that period they will go along pretty well to their fourth month, when they will again tend to heal over, and beyond that it looks as though there is less likelihood of closure occurring.

DR. FRANZ ALTMANN: I will just emphasize one point that Dr. Fowler discussed, *i.e.*, that no hearing improvement is, of course, possible unless there is a mobilization of the footplate. This mobilization is often achieved by manipulation

either on the neck of the stapes or the head of the stapes or the lowest part of the incus; in other cases, however, it is necessary to do manipulations on the footplate. These procedures are, however, not without risk. This was shown by a case which I operated a few months ago: on the table, after fracturing the footplate with the pneumatic hammer, an improvement of 35 to 40 db throughout the range with almost complete closure of bone air conduction gap was achieved. Although the patient was kept under antibiotics (achromycin 250 mgm. three times a day) he nevertheless developed a labyrinthitis on the sixth day and ended up with a completely dead labyrinth. This shows that we should give thought to the following: Are we justified in attempting to get a higher percentage of good results by increasing the danger to the patient? I think we are justified since stapes mobilization is still in the experimental stage. We will never be able to make real progress unless we take certain risks.

There is one more point. I was very interested in the improvement in hearing in cases where both crura were completely fractured. Our group in Presbyterian Hospital has given a great deal of thought to this; we feel it is difficult to understand how this could occur if both windows would vibrate in the same phase. Sometimes the fracture in the posterior crus might heal, particularly when no dislocation had occurred. In other instances blood clots might become organized in the round window niche; in this way the phase difference between the two windows could at least partly be restored. We even thought about reviving the old Hughson procedure, in such cases, and put a piece of muscle into the niche to give some sound protection to the round window.

DR. HOUSE: Dr. Bellucci will now give us his comments.

DR. RICHARD J. BELLUCCI: Before this wonderful symposium I thought I had something to say. I now find I cannot add much to the discussion. We have done a large series of cases at the Manhattan Eye, Ear and Throat Hospital and we have achieved 30 per cent good results in an unclassified group of patients. This is comparable to a similar group presented

here today. We have been using a very conservative technique and have experienced very few complications as a result of the mobilization of the stapes.

If we consider operating upon the footplate of the stapes we should attempt it as a primary procedure, so that the ossicular chain is not disturbed in any way. If we disturb the ossicular chain and go to the footplate after the crura of the stapes are fractured, then we will not obtain the maximum of improvement possible.

So far I believe we do not possess a technique which is safe to use at the footplate of the stapes. The footplate is in a very protected position, and the ossicles above it make the surgical approach very difficult.

We are in the process of developing an instrument which we hope will allow for better visualization and manipulation of the footplate. Until a more satisfactory technique is available for the surgery of the footplate I shall approach this phase of the work very carefully.

DR. HOUSE: Dr. Bellucci, I thank you, and will now ask Dr. Shea to comment.

JOHN J. SHEA, JR.: In reading the original literature on the subject of mobilization, my interest was aroused by a case reported by Jack of Boston in 1902.* As Dr. Meltzer pointed out, these original pioneers proceeded from where we are now in mobilization of the stapes to removal of it. This case was reported with good hearing ten years after bilateral removal of the stapes. There had been an adhesion between the eardrum and the oval window. It was reported that the patient could hear a soft spoken voice at 20 feet. That captured my imagination. I attempted to elevate the canal flap in such a way as to drop the drum on the oval window, but I could not do it, although I tried many times; also, in creating a long enough cuff I was afraid that if I left the drum down on the exposed

* Jack, F. L.: Supplementary report on a case of double stapedectomy operated upon 10 years ago. Tr. Am. Otol. Soc., 8:99, 1902.

oval window the patient might blow his nose and push it off. That was my first effort.

In addition I was very hesitant to do anything too vigorous about the footplate. It seemed to me most unreasonable to tamper with it or tap on it because of the ease with which it could be knocked loose. It was then that I decided that these two ideas could be combined. I decided to fenestrate the oval window. I selected a patient for this procedure on whom I had already done a successful mobilization of the other ear. She

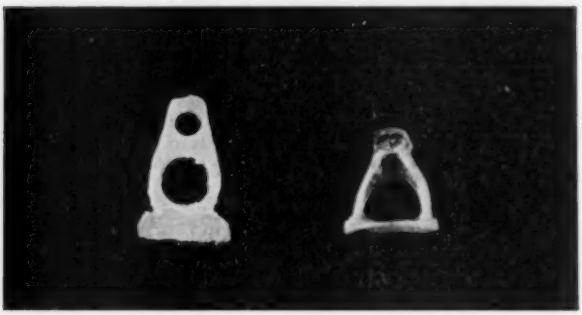

Fig. 1.

had a very marked hearing loss in this ear, down about 75 db for air and about 55 for bone. She was bothered by a blowing tinnitus. I exposed the bone in the usual way, attempted to mobilize it and I could not. I then removed the stapes and covered the oval window with a very thin skin graft, approximately .005 inch thick. I replaced the stapes with an artificial one I had created of nylon, from detailed studies of about 100 specimens. This artificial stapes was designed by a mechanical engineer who studied the stress problem involved, and strangely enough created one much like the original.

In Fig. 1 you can see the stapes I used. The human stapes from the base to the top measures about .140 inch. The one we created is the same height from the footplate to head. I

put an eye in the top of it to receive the end of the incus, to re-establish connection between the stapes and incus.

Fig. 2 shows the view from the top showing connection between the stapes and incus. In this case I was able to lay the artificial stapes right over the oval window.

I did this operation only several days before I left to come to the meeting, so I cannot report on the exact outcome. This is a completely preliminary report. Postoperatively, the woman was able to hear very well in the operated ear.

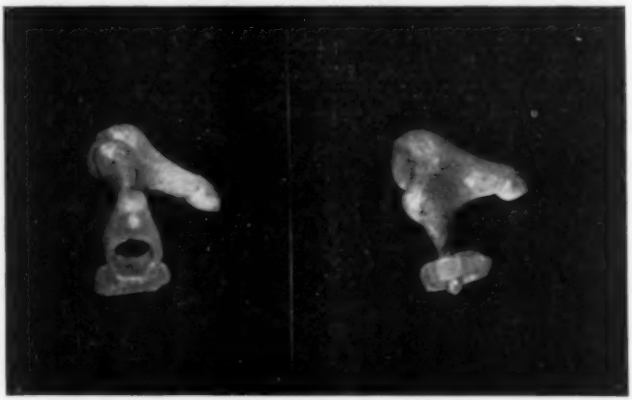

Fig. 2.

I have not tested her audiometrically. She had no useful hearing in that ear preoperatively, and recently her husband told me she was able to hear the gong of a church bell a quarter of a mile away, which she had not heard since she was a little girl.

DR. HOUSE: Thank you. These are all the variations of technique that are in the minds of many people regarding this operation. I should now like to ask Dr. Baron to discuss this symposium.

DR. SHIRLEY H. BARON: I should like to bring out just one point that has not been mentioned. It has been said that fenes-

tration can successfully follow mobilization, and that we know. It is not advisable, however, to fenestrate at the same operation should the mobilization appear to be successful. I present a case to show why one should defer the fenestration until a

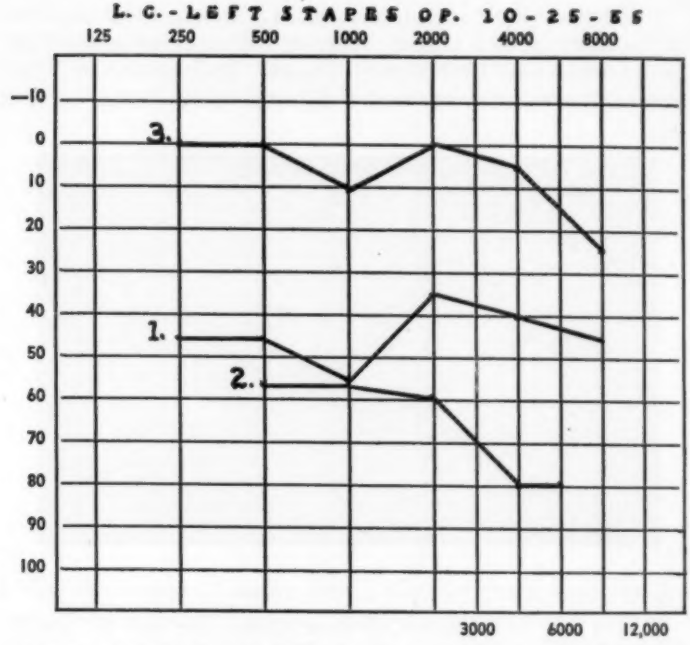

Fig. 1. 1. Preoperative Audiogram; 2. Postoperative Audiogram at surgery, following direct manipulation of stapedial footplate after crura had been fractured. Hearing appears to have been made worse, but recovery was spectacular as noted in audiogram 3, six weeks later. Conclusion: One should not fenestrate at the same operation if mobilization seems to have failed.

later date, in the hope that this may stop the tendency to do both procedures "in one sitting" as is currently the practice of a few otologists.

(Slide) This case proves that one cannot always tell at the time of surgery whether or not the attempted mobilization will fail. This is a 53-year-old female operated upon in October,

1955. The black line is her preoperative air conduction level. At surgery I fractured the crura, so I mobilized the footplate. The audiogram at surgery immediately following this, as noted by the green line, showed a very poor result. It looked

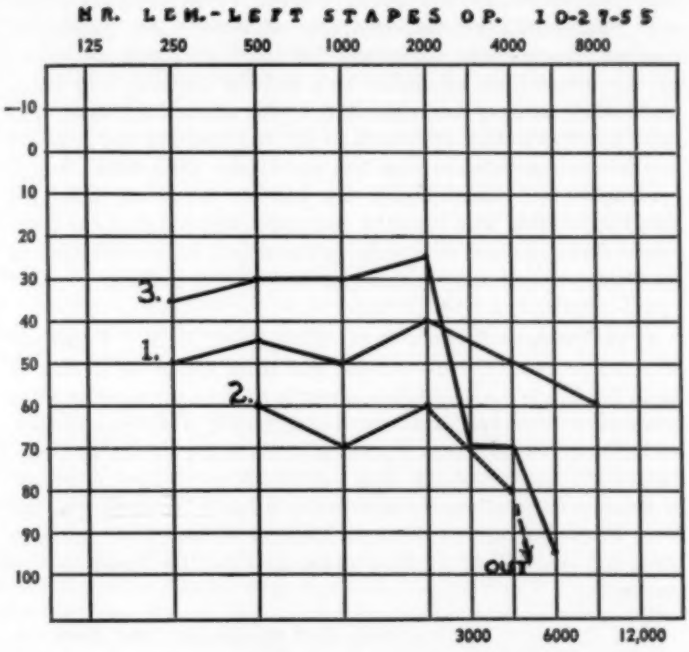

Fig. 2. 1. Preoperative Audiogram; 2. Postoperative Audiogram at surgery. Direct manipulation of stapedial footplate after crura were fractured. Note that frequencies above 4,000 are out; 3. Audiogram two months after surgery. Some improvement in frequencies from 250 to 2,000, but no recovery in high tones.

as though the hearing had been made worse; however, the actual postoperative result, shown by the red line, is excellent. The air-bone gap has almost been eliminated. This improved threshold was reached within two weeks after surgery and has been maintained ever since. The evidence here is clear that one cannot always tell at the time of surgery whether or not

the mobilization is successful; and that fenestration should be deferred until a proper conclusion can be reached.

(Slide) While the former case shows what can be done beneficially as the result of mobilizing the footplate directly, the slide of this case shows what might happen adversely. The black line shows the preoperative level. I fractured the crura, and then mobilized the footplate directly. An immediate marked hearing loss, especially for the high tones, as shown by the green line, resulted. This patient became very dizzy right after surgery and stayed dizzy for about four days. The red line shows that, postoperatively, the hearing did improve in the conversational range but not in the high tones, which became worse. Incidentally, the patient remained dizzy for about six weeks. The result in this case suggests that the traumatic force applied to the footplate might be transmitted to the basilar membrane in the first turn of the cochlea.

J. H. THOMAS RAMBO, M.D., New York, N. Y.: I had not planned to enter the discussion, but since the general idea of applying the drum membrane directly to the oval window after removal of the stapes has been brought up it is perhaps proper, and even necessary, that I make a preliminary report of a surgical technique directed to this end which we are in the process of testing, both clinically and in the animal laboratory at the New York University-Bellevue Medical Center. We are also studying the effects of this procedure on the inner ear in monkeys.

This technique differs from that which has just been described by Dr. Shea in that it does not use any free skin grafts or any prosthetic devices. It consists of an approach to the middle ear in the same manner as that described by Lempert and now used in stapes mobilization with the difference that initial incisions are made at the junction of the outer third and the inner two-thirds of the external canal so that the reflected canal skin from the posterior canal wall is longer. After reflection of the skin flap and the drum, an area of bone is removed at the Rivinian notch as in mobilization. The incus is then removed. With the drum folded forward one can obtain a very good exposure of the long handle of the malleus.

With a small golf-club spud, used to remove foreign bodies of the eye, the inner layer of the tympanic membrane surrounding the malleus handle is incised, and the malleus is separated from the drum. I first did this in 1953 in performing a modified radical mastoidectomy, as an aid to cleaning out pathology in the middle ear without destroying the ossicular chain. Since that time I have done this on a number of occasions in the operating room and many times on the cadaver. After a little practice it is surprisingly easy to do, without tearing the drum. After removal of the incus and the malleus the mucous membrane in the vicinity of the oval window is scraped away. When all bleeding is controlled and the middle ear is dry, the stapes is then removed from the oval window. The drum membrane, or adjacent flap skin, is placed over the oval window, invaginated, and the invaginated area packed externally with a small plug of cotton in the manner as described by Lempert in the fenestration operation. The skin flap attached to the drum is then replaced against the bony posterior canal wall to close the middle ear.

We then have a system for mobilization of the inner ear fluids which is the same as that following a fenestration operation except that we have substituted the oval window for a surgically made fenestra in the horizontal semicircular canal. The drum becomes plastered to the promontory, but there remains an air-filled tympanic space in the hypotympanum with free communication between the round window and the Eustachian orifice. We do not, of course, retain the advantage of sound transmission through the ossicular chain, but you have all heard the remarkable results given this morning, without explanation, when simple perforation or fracture of the footplate has been accomplished following fracture of both crura. Dr. Rosen has reported revisions in previous failures which yielded 34 per cent results of 30 db or better when a footplate approach was used. I believe that experience with the footplate approach in mobilization techniques is leading us inevitably to the recognition that hearing through even a small opening at the oval window is a much more physiological way for airborne sound to mobilize inner ear fluids; and we are, therefore, getting surprising good results when sound reaches

the inner ear through this natural route, even without an ossicular chain.

As I have observed these fracture techniques of the footplate, I have gradually overcome what has, for several years, been a stumbling block in my mind to the development of a predictable procedure for permanent hearing gain following stapedectomy. This has been the difficulty of removing a really fixed stapes. With the use of the percussion hammer, however, when it is necessary, I cannot now foresee any fixed stapes that could not be fractured and the two or more pieces hooked and pulled outward without injury to the inner ear. The advantage gained by separating the malleus from the drum, which can then be reflected forward to expose the entire middle ear, also allows infinitely better exposure for accomplishing this at the recessed stapes area.

In this symposium today we have been reminded by several of the participants that mobilization is not a standard procedure; that there are many techniques used; and that we are all looking for a special procedure which will offer a better solution to this surgery. I imagine that approximately the same situation probably existed following Miot's experiences with mobilization which prompted Jack in Boston, after repeating them, to perform stapedectomy. If such be the case, that we continue to follow faithfully the experiences of the otologists of over half a century ago, which we have done so far, we will again arrive full-circle to stapedectomy. Jack, however, was unable to find a way of closing the inner ear to obtain a successful hearing result and, because of the hazards of infection, abandoned the procedure. The technique which I have described may furnish the answer to what has been missing—a successful way to close the inner ear, while maintaining a functional tympanic space, following stapedectomy. I believe this will be the next logical step forward in otosclerotic surgery. Such a technique offers the same advantage as the fenestration operation in that it is a definite and predictable procedure. It offers the advantage of the mobilization approach in that it avoids a mastoidectomy and the problem of postoperative care. It, furthermore, assures a permanent hearing result in that it avoids the principal causes for

postoperative hearing loss of both operations. Since mobilization of inner ear fluids is through nature's own window, it will not close, and since the stapes footplate is removed, reankylosis of the footplate cannot be a factor after this procedure.

DR. LEWIS F. MORRISON: First of all to qualify myself, I do not do the fenestration operation. Secondly, I am in a teaching institution, and I have a certain amount of responsibility in regard to what may or may not be done by the members of the staff. Thirdly, I think I share with you a responsibility to the public. I would like either your assent or negation of the statement I often have to make that it is not correct for an individual who is not qualified to follow through with the fenestration procedure to do a stapes mobilization operation. If I am correct I would like to have some acclaim. If I am incorrect, please correct me.

DR. HOUSE: Thank you, Dr. Morrison. I am sure that this certainly does reflect the entire attitude of our panel. As I mentioned in the summary, I feel that this work is only a part of an otologic service that should be rendered to your patient; therefore, unless you are thoroughly familiar with temporal bone anatomy, thoroughly qualified in temporal bone surgery, I do not believe that you should undertake to render only a partial service.

If there is no other urgent discussion, I again turn the meeting back to our President, Dr. Lierle.

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PRESIDENT LIERLE: I cannot close this meeting without saying that I have known that this presentation has taken months

of good hard work, and I congratulate Dr. House and his panel on this most excellent presentation. I think it is one of the best we have had. I also thank the people of Montreal, including the men here, their wives and all the contributors who made this program possible.

SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY.

Washington, D. C., May 5-10, 1957.

The Officers and the Organizing Committee of the Sixth International Congress of Otolaryngology cordially invite you to attend the Congress which will be held in Washington, D. C., U. S. A., May 5 through 10, 1957.

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DEVELOPMENT AND ADULT ANATOMY OF THE AUDITORY OSSICLES IN RELATION TO THE OPERATION FOR MOBILIZATION OF THE STAPES IN OTOSCLEROTIC DEAFNESS.*†

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Chicago, Ill.,
and
THEODORE H. BAST, Ph.D., Med. Sc. (By invitation),
Madison, Wis.

I. INTRODUCTION.

It is a privilege to present those aspects of our study of the stapes which may be serviceable to the participants in the later symposium.

This report represents one phase of an inclusive, long-term investigation conducted under the auspices of the Central Bureau of Research of the American Otological Society. We take special satisfaction in the invitation of your President, Dr. Dean M. Lierle, to appear on this program, whereon laboratory research and clinical practice are to enjoy logical and helpful interrelationship.

Our concern now is with the structure of the stapes insofar as its architecture affects technical procedures calculated to mobilize the innermost member of the ossicular chain, ankylosed by spread of sclerotic bone into the normal space of the vestibular fenestra (oval window) and against the base (footplate) of the stapes.

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* Read at the Sixtieth Annual Meeting of the American Rhinological, Laryngological and Otological Society, Montreal, Canada, May 15, 1956.

† Contribution from the Department of Anatomy, Northwestern University Medical School (Contribution 624), and from the Department of Anatomy, University of Wisconsin.

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It is a striking fact that even a relatively sturdy stapes is still a congenital weakling, a veritable wraith when compared to its earlier self in the midterm fetus. The normal steps in development account for stapedial fragility; they are basic to whatever may be said about adult structure.

It is fair to regard the stapes as a "nonconformist among bones." The incus might justifiably be placed in the same category, but for different reasons; in fact, the three ossicles originate in an exceptional way, continue on a course of morphogenesis which is not only noncompliant, but also precipitate, to attain adulthood before the infant is born.

II. OBSERVATIONS AND DISCUSSION.

Even as early as the second month of intrauterine life (8½ weeks, 28 mm.), the future ossicles are already formed in cartilage, distinguishable from the elements of the branchial skeleton from which they were derived, in relation to the mandible.*

This means that in the course of their morphogenesis as cartilaginous, and later as osseous skeletal elements in vertebrates, the ossicles must undergo a remarkable transformation. Their predecessors functioned as supports for the respiratory mechanism in aquatic and amphibious vertebrates; in mammals they are made over to serve as links in an ossicular chain.

A. *Developmental Stages Shown by Reconstructions.*

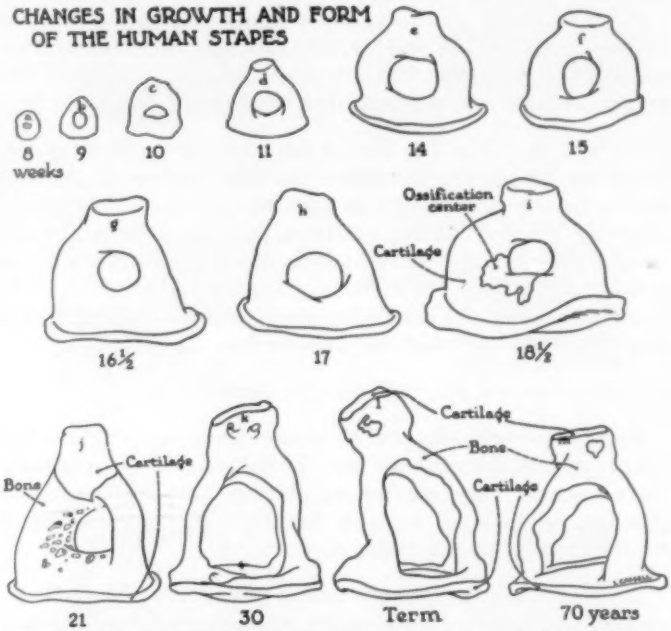
When first distinguishable, in the fetus of eight weeks, the "stapes" is not yet stirrup-shaped (see Fig. 1-a);** rather, it is a ring.

Within the short period of a week (see Fig. 1-b), the characteristic portions are identifiable, but more prominently still (see Fig. 1-c) one week later (11 weeks, 78 mm.) and in slightly older specimens (see Figs. 1-c and 1-d).

* See Fig. 144, the present authors' monograph, in "The Temporal Bone and the Ear" (C. C. Thomas, Springfield, 1949).

** Figs. 1-a to 1-m are used here in place of several lantern slides which accompanied the presentation of the paper; the remaining figures (2-a to 2-f, 3-a to 3-d, 4-a to 4-f, 5-a to 5-c) were prepared as contact prints of lantern-slide negatives actually shown during the reading of the paper.

At the close of another period of growth, three weeks in length, the ossicle is a stirrup (see Fig. 1-e). Soon the base of the stapes becomes lipped; the head is foveate to accommodate the lenticular process of the incus (see Figs. 1-f to 1-h).



Figs. 1-a to 1-m. Drawings of reconstructions of stapes. Specimens selected to demonstrate eleven successive stages in morphogenesis (fetal stage indicated in weeks) and to show variability in form and size of mature ossicles in the fetus at term and in an adult of advanced age. (From Anson and Cauldwell: Quarterly Bulletin of Northwestern University Medical School, 15, 263-269, 1941.)

In the 18-week fetus ossification has begun, in a solitary center on the obturator surface of the base (see Fig. 1-i).

The progress of ossification is rapid. Within a period of three weeks, bone has spread along the crura; upon reaching the neck of the ossicle, bone has become continuous circumferentially. Growth thereupon ceases (see Fig. 1-j). Ossifi-

cation involves excavation, a process which serves to alter profoundly the structure of the ossicle.

In the stapes of the fetus of 30 weeks, periosteal bone has been removed on the obturator surface of the base, in the crura and neck (see Fig. 1-k). As a result, the stapes has been hollowed throughout. Cartilage now remains only on the articular surface of the ossicle and on the vestibular and fenestral aspects of the base. The addition of endochondral bone has converted the base and the head into two-layered plates.

At term (see Fig. 1-l) and in the adult (see Fig. 1-m) cartilage persists on the vestibular (medial) surface of the base and on the fenestral margin as a peripheral rim. The tympanic (lateral) surface, on the contrary, is formed by a plate of irregular bone which is composed of both endochondral and perichondral tissue. The crura are deeply channelled. The head and neck of the ossicle are strikingly eroded; the capital extremity, like the basal end, is bilaminar.

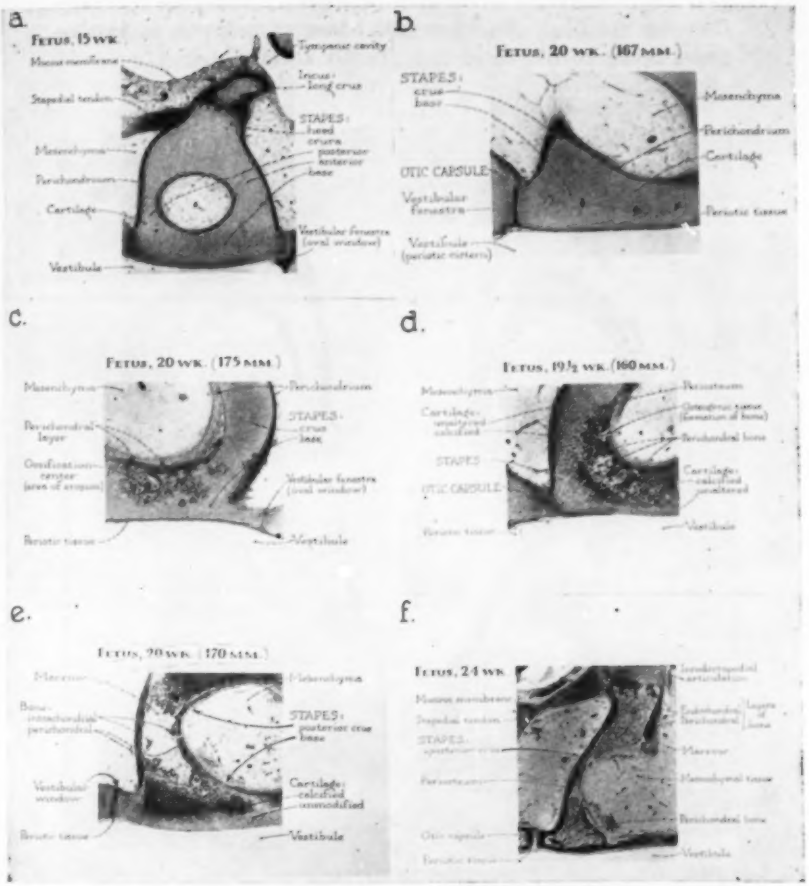
B. *Developmental Stages Shown by Sections.*

Reconstructions, like the 13 whose changing structure has been reviewed, demonstrate the "gross" fate of the originally bulky ossicle. They require supplement, through the use of photomicrographs, to account for the histological processes involved in the transformation.

Near the beginning of the fourth month (112 mm.) of intra-uterine life, the future ossicle has acquired characteristic form; however, it is composed wholly of cartilage (see Fig. 2-a).

In the stapes of the 20-week (167-mm.) fetus, ossification is merely predicted in the vacuolization of the cartilage on the tympanic (or obturator) aspect of the base (see Fig. 2-b). The altered cartilage is distinctive, the line of separation from the unmodified portion (indicated by arrows) being that which subsequently divides an osseous from a cartilaginous layer on the stapedial base.

In another specimen of approximately the same stage, and to the depth previously indicated, bone-formation extends in

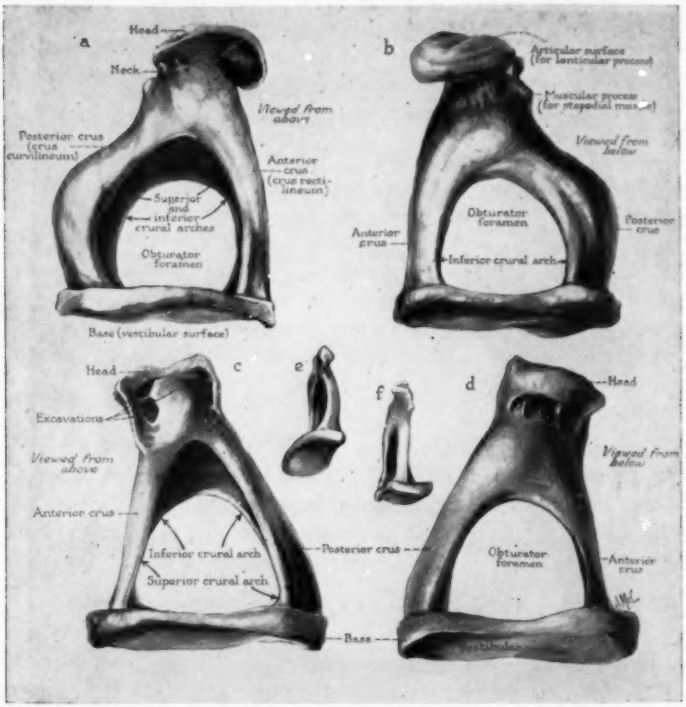


Figs. 2-a to 2-f. Photomicrographs of transverse sections through the stapes. Showing the primordial histological structure of the stirrup, and steps in the conversion to bone. Fig. 2-a, entire ossicle; Fig. 2-c, anterior crus and base; others, posterior crus and base.

the solitary ossification center (see Fig. 2-c). Perichondral bone is being produced on the surface, while erosion is occurring at deeper level.

Removal of cartilage is now a striking feature (see Fig.

2-d). Heralding the advance of osteogenic tissue, the cartilage becomes calcified. Perichondral bone, as a layer, is incomplete, being destroyed as it is freshly formed.



Figs. 3-a to 3-d. Photomicrographs, continued. Fetal; infantile and adult structure of the ossicle.

Where the process of ossification is furthest advanced (mid-length of the crus), perichondral bone forms a complete shell (see Fig. 2-e). Endochondral bone, transitorily formed, has been removed, and is replaced by marrow. The crura are now hollowed columns of perichondral bone, which contain mere remnants of old cartilage and newly-formed marrow.

In a specimen of 24 weeks (see Fig. 2-f) the obturator wall is a mere remnant (resorbed between the marking arrows). Marrow, now openly exposed to the mesenchymal tissue, will be replaced by the submucosal layer.

The full effect of this developmental process is demonstrated in the fetus of four and one-half months. Throughout the length of the crus, the mucous membrane occupies the former marrow-space of the ossicle, resting against the surface of the crus which was once internal.

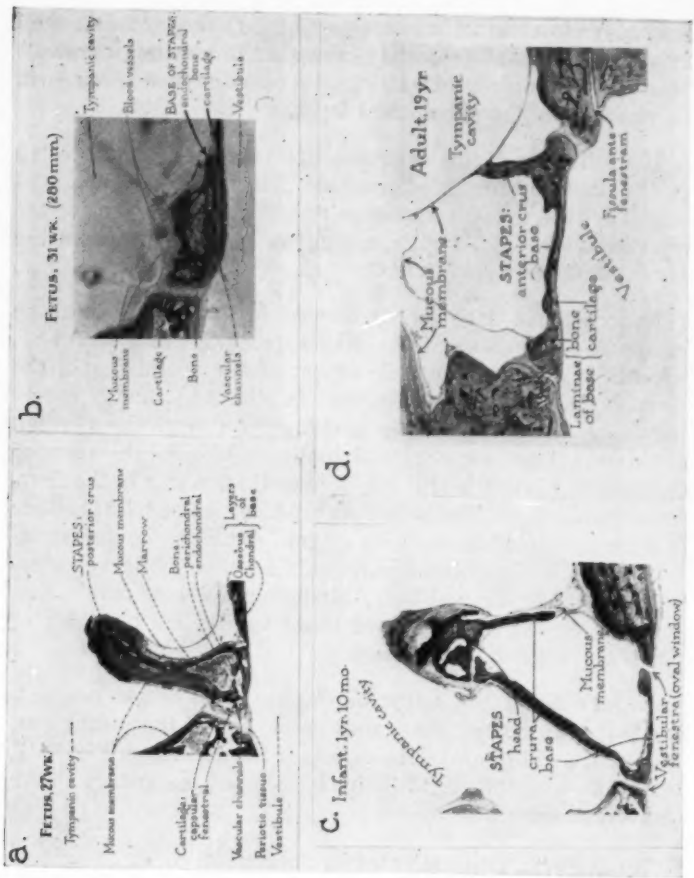
Endochondral bone, newly-formed in apposition with the cartilage of the base of the stapes (see Figs. 3-a and 3-b), spreads across the tympanic aspect of the footplate (in the direction of the unlabelled arrow, in Fig. 3-b), finally covering the eroded surface of the cartilage. Although the addition of this new layer sometimes virtually doubles the thickness of the base, the latter is still far thinner than it was in the four-month fetal stage. The bone thus produced is not solid; neither is it evenly spread through its extent. Actually, the accumulation is thick circumferentially and is quite highly vascularized (see Figs. 3-c and 3-d). Numerous intercommunicating channels occur; the contained blood vessels are branches of those in the submucosal tissue.

As a result of the action of the processes whose progress has just been traced, the stapes in the ear of the infant (see Fig. 3-c), and therefore, the ossicle of the adult (see Fig. 3-d), bear little resemblance to their ring-shaped forerunner in the eight-week fetus.*

C. *Adult Form, Demonstrated by Specimens.*

It now remains to account for the adult form and size of the stapes. This will be done through the use of excised and "cleaned" specimens, drawn by the artist—as the ossicles were seen through a high-power binocular microscope. Four selected specimens will suffice for an introductory description.

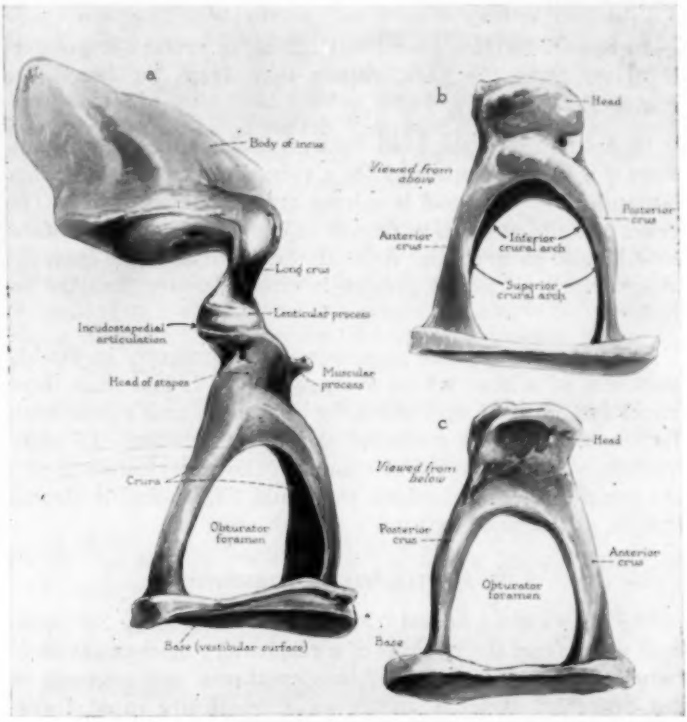
* Detailed and amply illustrated accounts of the morphogenesis of the auditory ossicles may be found in the following journal articles by the present authors and in related publications cited therein: Annals of Otology, Rhinology and Laryngology, Vol. 55, pp. 467-494, 1946, and Vol. 63, pp. 394-434, 1954; Quarterly Bulletin of Northwestern University Medical School, Vol. 28, pp. 17-45, 1954.



Figs. 4-a to 4-f. Drawings of excised, "cleaned" specimens of adult stapes (Figs. 4-a and 4-b, Specimen I; Figs. 4-c to 4-f, Specimen II).

In Specimen I the head of the stapes is deeply pitted, as is often the case. The head, relatively large, is inclined anteriorly (see Figs. 4-a and 4-b). The muscular process is fairly prominent; it is attached to the neck (as in 75 per cent of cases), not to the head proper. The superior crural arch (toward the observer in Fig. 4-a) is more expansive than the in-

ferior (viewed in Fig. 4-b); it is roughly triangular, whereas the inferior one is ovoid. Here, as usual, the anterior crus is the more slender of the two and the straighter (hence the term, *crus rectilineum*). The posterior crus is curved in this instance, as it most frequently is (so, the term *crus curvilineum*).



Figs. 5-a to 5-c. Drawings of specimens, continued. Fig. 5-a, Specimen III; Figs. 5-b and 5-c, Specimen IV.

In Specimen II the head meets the crura in an even curve. Like the preceding example, the head is deeply pitted (see Figs. 4-c and 4-d). The articular surface is foveate. The crura, deeply channelled and having crural arches of differ-

ent dimensions, are less sturdy than those of the other specimens. The posterior crus is almost straight. Both the posterior crus (toward the observer in Fig. 4-e) and the anterior crus (facing the observer in Fig. 4-f) originate from points nearer the inferior than the superior margin of the base. In this specimen the crura meet the base at almost a right angle; however, this angle of junction may be acute, either superiorly or inferiorly.

In Specimen III a prominent muscular process is present; it arises from the neck, rather than from the head (see Fig. 5-a).

In Specimen IV the head is large and quadrilateral in outline; it is inclined anteriorly to a very slight degree (see Figs. 5-b and 5-c). The head is sulcate across, but not pitted. The crura are almost equal in respect to curvature (and, therefore, length) and to strength. As is almost invariably the case, the superior crural arch is greater in circumference than the inferior.

The outcome of these processes is the presence, in the human ear, of a bone whose average weight is less than three mgms. (2.86 in 75 specimens, to be exact), and whose adult form would suggest profound skeletal emaciation. To make matters worse (from the viewpoint of the otological surgeon), the ossicle is weakest where we would like to find it strong, that is, at the basal extremity of each crus.

III. SUMMARIZING STATEMENTS.

The stapes is the oddest bone in the human body. Salvaged, as it were, from the remains of a respiratory mechanism functional in aquatic and amphibious creatures, this segment of the branchial skeleton undergoes dramatically rapid transformation to become a stirrup-shaped ossicle of full adult dimensions just as the human fetus passes through the middle month of its intrauterine life. The stapes is as mature several months before the infant is born as a tibia (for example) is in a person 20 or more years of age; the stapes lacks the usual mechanisms which cause lengthening and thickening in a typical long bone of the human skeleton.

Histologically, the constituent bone of the stapes is primitive; it is never replaced by tissue of Haversian type.

The transformation which converts the crura into channelled columns, the head into an excavated cylinder with a bilaminar articular extremity, and the base into a thin, two-layered plate results in striking reduction in bulk. The several parts are excavated, and the space thus exposed is made continuous circumferentially to face the obturator foramen—the latter space being greatly enlarged at the expense of that which originally contained marrow and endochondral bone. The surface of bone thus exposed by erosion is draped by mucous membrane; blood vessels in a submucosal position communicate with others which course peripherally in the endosteal bone of the head and of the base.

In cases of otosclerosis, with threatened ankylosis of the stapes, the features just described assume critical significance. Circumstances of this kind, dependent, as has been demonstrated, upon normal morphogenesis of the stapes, are basic to the challenge which confronts the otologic surgeon in the effort to restore mobility of the stapes.

Reduced to the status of a skeletal ghost, the stapes, in the otosclerotic patient, awaits the inexorable advance of pathological bone from the wall of the window in which it rests—with inescapable and deforming ankylosis.

STRUCTURES OF THE SPIRAL PROMINENCE AND EXTERNAL SULCUS AND THEIR RELATION TO THE ORGAN OF CORTI.*†

MERLE LAWRENCE, Ph.D. (By invitation),

Ann Arbor, Mich.

Much of the confusion that presently exists in the interpretation of the physiological activities of the inner ear is the result of insufficient information concerning the morphology of the structures involved. The truth is that all the facts are not yet in, and since the number of theories seems to vary inversely with the number of established facts, we are today confronted with a myriad of possibilities concerning the activities within the cochlear duct.

Many "explanations" of the mechanism behind pathologic processes within the inner ear are based upon notions of endolymph flow and constitution, and the structures on the "lateral"‡ wall of the cochlear duct, whether absorbing or secreting, are always assumed to play a part. Such hypotheses will remain purely speculative until they are founded on more exact knowledge of the anatomy found within the scala media.

This paper describes structures within the region of the *prominentia spiralis* which have not previously been reported; structures which may play a very important, if not the major, role in the provision of nutrient material to the cells of the organ of Corti.

The present day conception of this region stems from the report by Shambaugh[1] in 1908: a description of the anatomy of the external sulcus in which he observed a small tubule sug-

* Read at the Sixtieth Annual Meeting of the American Laryngological, Rhinological and Otological Society, Inc., Montreal, Can., May 15-17, 1956.

† From the Physiological Acoustics Laboratory, Institute of Industrial Health, and Department of Otolaryngology, University of Michigan. This research was supported in part by the Research and Development Division, Office of The Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-634.

‡ This use of the term lateral refers to a direction away from the modiolus: part of the time this would be medial with respect to the skull.

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gesting a secretory function of the cells. Subsequently this has been called Shambaugh's gland. To the time of the discovery of this tubule the establishment of a secretory function for this area has had a turbulent history, but as is usual, attempts to settle a theoretical argument led to more accurate observation and the elucidation of morphological facts.

The problem really starts in 1836 with the publication by Breschet,[2] a monumental work in which he describes the substance which is inserted into the spiral groove of the bony capsule. Upon dissection this appears as a gelatinous tissue connected between the bony wall and the basilar membrane which Breschet called "the yellow band," or "membranous belt."

A decade later Todd and Bowman,[3] in a textbook filled with original notions, decided that this structure to which the basilar membrane was attached was a muscle that might serve the purpose of accommodation similar to that of the eye, but they felt that, more than likely, "this very interesting structure—[is] placed there to defend the cochlear nerves from undue vibrations of sound."

Then followed a period of the most careful dissection and observation with low magnification, the high point of which was the classic description by Corti[4] of the organ which now bears his name. One of the earliest observers was Kölliker[5] who described in some detail the cells that made up this "cochlearis muscle" of Todd and Bowman, and pointed out that no "Faserzellen" as seen in elements of involuntary muscle could be found. Corti agreed with this, but described another type of cell that was different from the connective tissue cells. He left the question open as to whether or not the structure was a muscle, and used Kölliker's name for it, *ligamentum spirale*.

Claudius[6] described the cells lying along the scala media side of the basilar membrane, a layer of cells extending from the tall mound of Hensen cells on the "lateral" end of the organ of Corti to the concave region between this layer and the spiral prominence. The cells, which had puzzled Corti, were found by Deiters[7] to lie in this concavity of the spiral ligament, and

he described them as distinct from those of Claudius, being cylindrical with processes extending into and appearing bound to the connective tissue substance. Boettcher[8] followed Deiters, referred to the furrow as the sulcus and gave a more detailed description of these cells, referring to them as "root-cells." They have since been known as the cells of the external sulcus.

There have been many descriptions of these cells since, but the main difference among observers has been in the interpretation of their function. Boettcher did not specifically say that the spiral ligament was a muscle, but he did say that it was conceivable that these cells of the external sulcus could have contractile properties operating through fibers, which he described earlier,[9] lying above Claudius cells and connected to the reticular membrane. On the basis of this he was described, by Shambaugh, as supporting Todd and Bowman in the muscle theory; but in a paper, 18 years later[10] Boettcher vehemently denied ever having been in favor of the idea of a cochlear muscle, and had only mentioned the possibility of these cells having contractile properties as a speculation, but offered no evidence.* Actually Todd and Bowman, and later Boettcher, were referring to different structures; the former were referring to the entire area of what we now call the spiral ligament, while Boettcher referred to the row of external sulcus cells which had not been described at the time of Todd and Bowman.

Following the careful description of these cells by Boettcher there were several more (Gottstein,[11] Prenant,[12] Katz,[13] Retzius,[14] and others), some backing the thought that the cells possessed contractile properties and others emphasizing that there was no real evidence for this view. Gottstein offered the opinion that these cells represent a neuroepithelium, but could find no nerve fibers connecting with them.

This brings us up to the description given by Shambaugh[1] which has been accepted as the final word for almost 47 years. He studied the labyrinth of the domestic pig, and stained by Mallory's method. This showed the group of epithelial cells

* I am indebted to Dr. Stacy R. Guild for having called my attention to this later article by Boettcher.

that occupy the deep part of the *sulcus externus*, clearly distinguishing them from the adjacent cells.

As the earlier observers had noted, these cells send long finger-like processes deep into the spiral ligament. The cells do not form a continuous band spiraling around the turns of the cochlea but appear in a clustered arrangement. Between these clusters the lining epithelium exists as a simple layer of cuboidal cells similar to those which cover the surface of the spiral prominence. Occasionally there is a cavity at the open surface of the external sulcus where many epithelial cells penetrate the spiral ligament. This shows up most clearly when the section is made at right angles to the modiolus. It is quite possible that Boettcher[8] also saw these, but thought that they were openings left when he pulled the finger-like cells from their recesses, which some of them probably were. Within this epithelial bundle there frequently appears a small but clearly defined tubule. This is very fine and is located in the center of the epithelial cell-filled cavity. In the pig these could be found only in the basal turn of the cochlea.

Because of the presence of this tubule and the extreme vascularity of this region, Shambaugh designated this area as the principal source of endolymph and later[15] suggested that the stria vascularis (generally accepted since Corti as the source of endolymph) is merely a mechanism for producing pulsation in the endolymph bringing about the "continuous flow of tonus impulses to the skeletal muscles which clearly emanate from the cristae."

The observations reported here are only of the spiral prominence and external sulcus, and came about by chance when a silver stain being used with celloidin-embedded sections for the study of nerve fibers turned out to reveal the fibers of the basilar membrane, and the cells of the external sulcus and the spiral prominence.

MATERIAL AND METHOD.

During the course of a study carried out by Dr. J. H. T. Rambo at the Lempert Institute of Otology in New York and

sponsored by the Lempert Research Foundation, several Rhesus monkeys were perfused intravitally with Heidenhain Susa fixative. The temporal bones were removed, processed, embedded in celloidin and sectioned. A number of random sections were made available to us for experimenting with various silver stains.

The stain used on the material presented here is a modification of the Bodian silver method. Since all the staining was experimental no two sections received exactly the same treatment. The main variations consisted of the time they were left in the protargol solution, the time left in the gold chloride solution, if used, and an occasional substitution of analine oil for oxalic acid. Actually, none of these variations seemed to change the picture to any great extent, the manner in which the tissue takes the stain having already been determined by the acid in the fixative. If a fixative containing no acid is used this stain is specific for nerve fibers and cell nuclei, but when acid is used in the fixative, all tissues are stained, particularly the fibers of the basilar membrane.

OBSERVATIONS.

A clear distinction must be made between the cells of Claudius and those of the external sulcus. The Claudius cells are cuboidal or sometimes columnar. They are uniform, distinctly shaped, and clearly nucleated, resting upon the fibers of the basilar membrane and extending from the tall columnar Hensen cells on the "lateral" side of the organ of Corti to a region beneath the bulging spiral prominence. At this point the external sulcus cells are encountered, and with most stains are clearly distinguished from the Claudius cells. These cells of the external sulcus not only take a deeper stain but they also have long slender processes that extend well beyond the basilar membrane fibers which serve as a base for the Claudius cells. These processes, however, cannot always be seen with conventional stains, but become easily perceptible when a silver stain following an acidified fixative is used*; also with this treatment many other features are revealed.

* Retzius[14] was the first to demonstrate these by means of a silver stain.

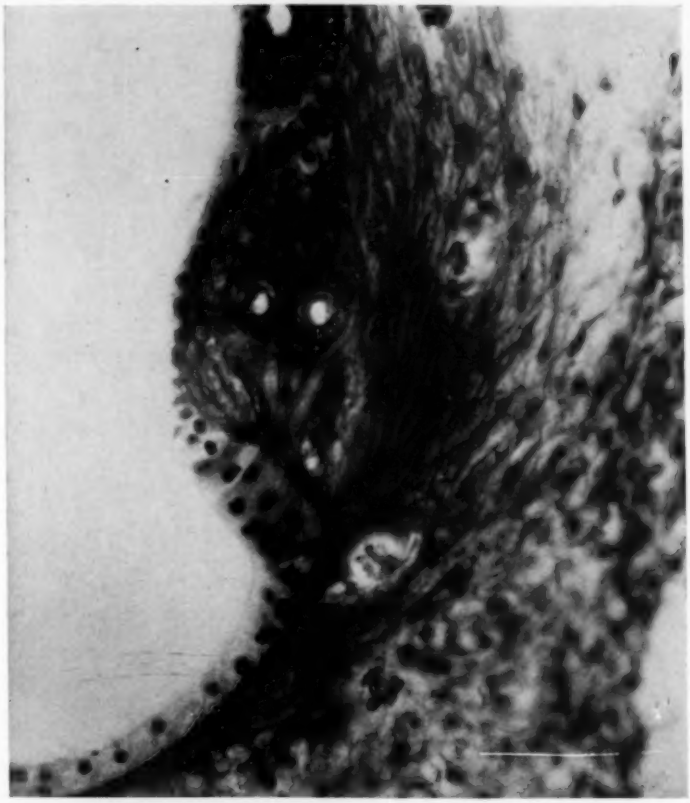

Fig. 1. The external sulcus cells and spiral prominence as seen in the Rhesus monkey. The cells of the external sulcus show long processes that extend between and around capillaries within the spiral prominence. A bundle of fibers from the basilar membrane branches off to form a hand-like grip on special cells (see Fig. 4) in the lower outer portion of the bulge. Monkey 142R-277 x 470.

Figure 1 shows the root-like processes of the external sulcus cells as they extend into the spiral prominence. The early observers, particularly Retzius[11] described these processes as extending back into the spiral ligament. Prenant[12] had also suggested that it was not improbable that the processes of one cell anastomosed with those of another, but Retzius could find

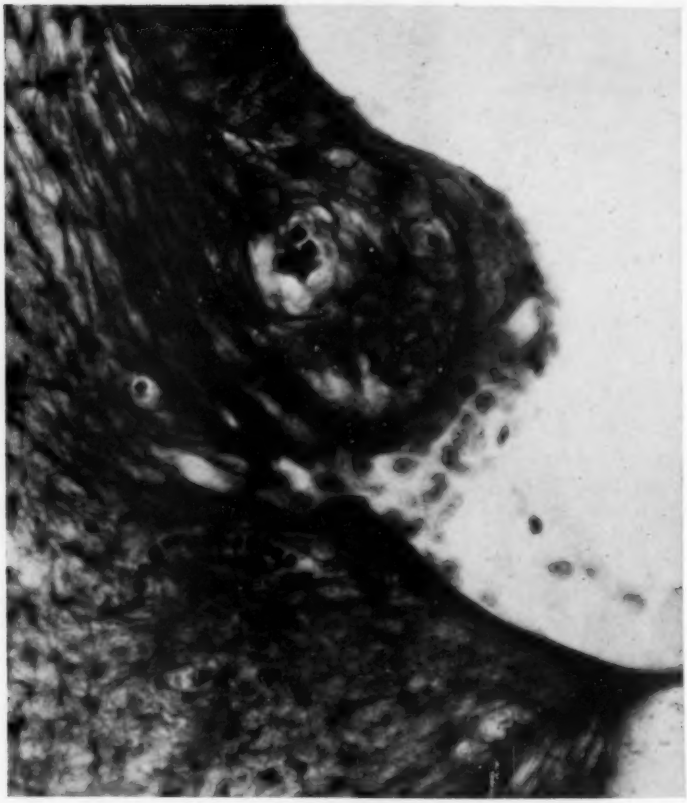

Fig. 2. The opening from the external sulcus into the region behind the spiral prominence. These lie between the bundles of basilar membrane fibers shown in the previous figure, and are filled with cells. It is through these cells that Shambaugh's tubule passes. There is an indication of such a structure in this section, but it does not show up in the reproduction. Monkey 141L-222 x 490.

no evidence for this. It was also stated (Retzius) that the muclei lie well back in the region of the spiral ligament.

In the material examined here these particular cells extend their processes into the spiral prominence rather than the spiral ligament. The distinction between the two is not hard to make when the continuing fibers of the basilar membrane

are stained as distinctly as in these sections. It is also apparent that there is no observable anastomosis between cell processes, and that the nuclei lie well toward the external end. The openings which these processes appear to go between and around (see Fig. 1) are small capillaries. In describing the position of the nuclei and the direction of extension of the processes the earlier anatomists must have confused these cells with the epithelial cells that Shambaugh described as containing a tubule. There are openings occurring every now and then which extend in channels under the spiral prominence and back into the spiral ligament. These appear filled with epithelial cells as described by Shambaugh and shown in Fig. 2. There are, then, two distinct types of cells which alternate in occurrence around the spiral of the sulcus. It is in the midst of these epithelial cells that Shambaugh saw the tubule. Although our material has not revealed a tubule as clear cut as that of Shambaugh, who resorted to sections horizontal to the coil of the cochlea rather than vertical to it (parallel to the modiolus) the section of Fig. 2 shows an indentation and line between cells which closely resembles the diagram published by Shambaugh.

In this photomicrograph (see Fig. 2), below the opening in the sulcus, a capillary large enough to allow only the passage of a single red cell at a time can be seen. In the middle of the spiral prominence is a larger vessel cut in cross section and containing several red cells.

As noted in all previous investigations this region is highly vascular, containing many capillaries of various sizes. Fig. 3 shows a large branching capillary extending from the bulging region of the spiral prominence deep into the spiral ligament with another branch reaching up toward the region beneath the stria vascularis. Another is seen below the point where the main branch of fibers separates from the basilar membrane to extend into the spiral prominence.

If a section is made at right angles to the modiolus so the cut is made through the bulge of the spiral prominence, or occasionally with a cut parallel to the modiolus, the hook of the basal turn twists so that the prominence is cut essentially in the same way, the relation between the capillaries and the

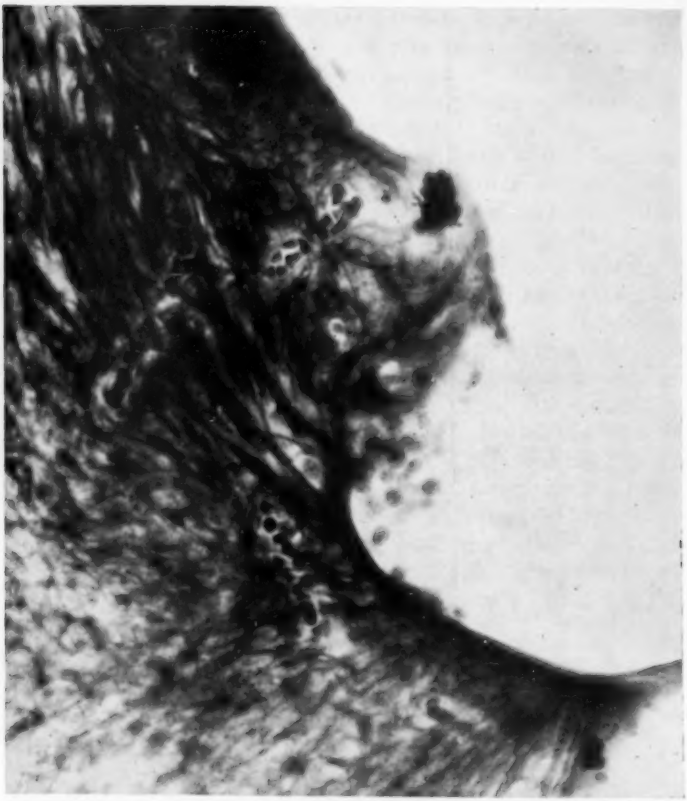

Fig. 3. A picture of the spiral prominence to show the vascularity of the area and the infiltration by the fibers from the basilar membrane. The capillaries can be distinguished by the presence of many red cells. Monkey 141L-225 x 530.

"root-cells" can be determined. These capillaries spiral around with the prominence but undergo much looping and twisting; at the same time they go over and under the processes of the "root-cells" much in the manner of the fibers of a woven mat.

The fibers of the basilar membrane as they split up just behind the external sulcus are distinctly revealed in these sections. In Fig. 1 the basilar membrane is the dark line curving

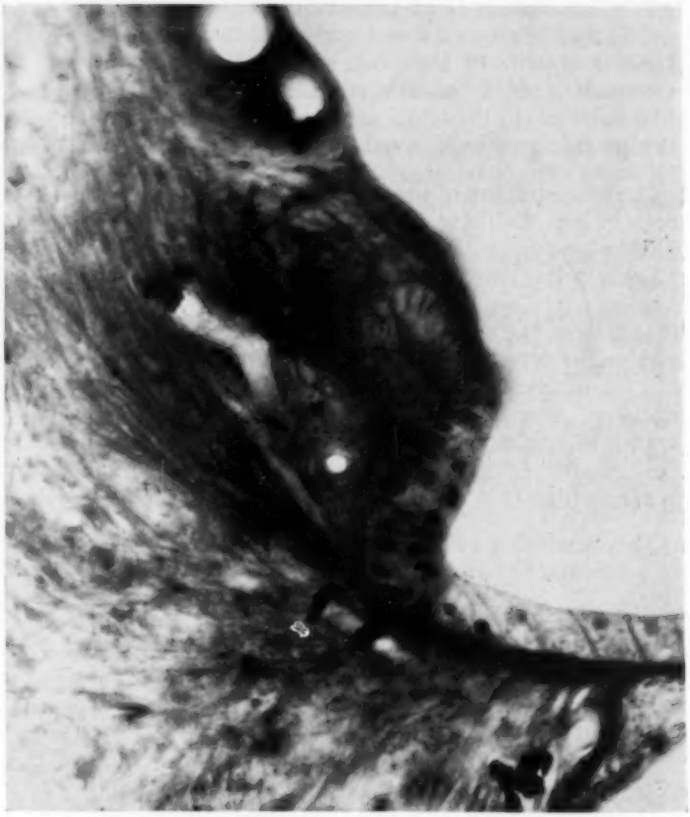

Fig. 4. Here is shown the branching bundle of fibers from the basilar membrane going to the group of cells which appear clustered in the form of a rosette. The external sulcus cells and their nuclei can be clearly distinguished from the Claudius cells. Monkey 142L-331 x 475.

up from the lower left. Upon reaching the region of the external sulcus cells there is a distinct branching of the fibers. One branch extends into the structures of the spiral prominence and the other breaks up into many more, extending up and out into the connective tissue of the spiral ligament. These latter fibers are very extensive, some going behind the stria vascularis and extending to its other end. The branch to the

spiral prominence is of particular interest. It divides quite profusely and appears as a complicated snarl around the capillaries and cells of the prominence. A regularly occurring termination of the basilar membrane fibers appears as a hand-like structure in the lower portion of the bulging prominence. Within this meshwork a cell nucleus can be seen.

A clearer picture of the true nature of this structure can be seen in Fig. 4. These fine fibrils from the basilar membrane intertwine among a rosette of cells. There appear to be 10 to 12 cells in this rosette which, since they do not appear in every section, probably do not continue as a tube spiraling around the turns of the cochlea but occur rather periodically. In this section the type of external sulcus cell that has the processes can be distinguished clearly from the Claudius cells and the nuclei of several "rosette" cells stand out distinctly. The branch of basilar membrane fibers extending to and invading the "rosette" cells can also be seen. We have seen these cells in the basilar turn only.

This branching of basilar membrane fibers does not occur as a continuous band around the cochlea behind the external sulcus. The branches are in groups like fingers on a hand but unite again as they approach the clusters of "rosette" cells. Within the regions where these fibers separate the second type of external sulcus cells (epithelial cells) appear and in sections through this region (see Fig. 2) one sees a picture almost identical with the drawings presented by Shambaugh.

DISCUSSION.

Shambaugh's observations are completely supported by the material used in this study. In addition there have been revealed within the spiral prominence, clusters of cells appearing in the form of a rosette infiltrated by fibers which show a direct continuation with the basilar membrane. There is evidence here to suggest a functional relationship between the basilar membrane and the structures of the spiral prominence.

It is conceivable that the "rosette" cells provide a needed nutrient material which is released or forced out when the interwoven fibers from the basilar membrane are put into ac-

tion by vibrations entering the cochlear fluids and moving the basilar membrane. The observations of Crowe, Guild and Polvogt[16] are quite significant in this connection. They found a deterioration of the external sulcus cells whenever there appeared a deterioration of the organ of Corti. Specifically, they never observed a deterioration of the organ of Corti without deterioration of the external sulcus cells in the same area, but in some instances the deterioration of the external sulcus cells extended beyond that of the organ of Corti. This led them to suggest that the external sulcus cells play a role in the providing of nutrient material to the cells of the organ of Corti and that if these failed the organ of Corti in that region deteriorated; failure of function of the external sulcus cells occurs first. The intimate relation between the fibers of the basilar membrane and the structures of the spiral prominence suggest that the more active a particular region of the basilar membrane, the more nutrient material forced from the "rosette" cells. Perhaps the stria vascularis merely provides a constant supply of endolymph to serve as a medium for the special nutrient material.

There is still no obvious explanation of the function of the cells with the long processes found in the external sulcus, although when seen over their entire length they seem to be associated with capillaries. There is no function other than secretory, as proposed by Shambaugh, suggested for the epithelial cells and the accompanying tubule that fills these periodic gaps in the external sulcus.

In mapping out the intricate vascular system of the spiral ligament Smith[17] describes an extensive network in the spiral prominence. Large arterial vessels enter this region, and the smaller vessels form a narrow band spiraling around with the prominence. We have here described the manner in which the vessels weave in and out among the "root-cells." Smith has pointed out that the network in the stria vscularis, the spiral prominence and upper and lower portion of the spiral ligament are separated by vascular supply and drainage. Small variations in circulation are possible so that disturbances may be confined to one area without necessarily spreading to another. Seymour[18] and Irwin, Weille and Burrage[19] have de-

scribed such regional disturbances in response to drugs. This possibility, coupled with the findings reported here, points to a mechanism for the control of nutrition to the organ of Corti.

Obviously we do not yet know all about the structures of this region, but by further use of these special staining procedures perhaps more details can be revealed.

Much credit is due Miss Maxine Clapper for her tireless technical assistance in the processing of the material presented here.

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SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Arrangements have been completed for the joint meeting of the North Carolina Society of Eye, Ear, Nose, and Throat, and the South Carolina Society of Ophthalmology and Otolaryngology September 17, 18, 19, 1956. Headquarters will be the George Vanderbilt Hotel, Asheville, North Carolina.

An unusually attractive program has been arranged, and a large attendance is anticipated.

Asheville, North Carolina, is in the mountains of Western North Carolina, and is a particularly beautiful spot in this season of the year.

For further information write Roderick Macdonald, M.D., Sec. and Treas., 330 East Main Street, Rock Hill, S. C.

FACTORS AFFECTING HEALING FOLLOWING TEMPORAL BONE SURGERY.*†

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I. INTRODUCTION.

Following surgery of the temporal bone the tendency is for healing to take place in keeping with the natural proclivity of all wounds to heal; nevertheless, even under the best of conditions, the process is slower here than in other regions of the body because of the very nature and location of the postoperative mastoid wound. This comparative slowness of healing, so long as it remains consistent in its progress, does not, however, constitute a problem. In the majority of cases, under competent care, healing is not unduly prolonged. The problem, in postoperative care, arises in the minority group of cases in which there is marked delay or complete arrest in the progress of healing. In such cavities, discharge may persist for many months or even years. This discharge is due to the influence on healing of certain fundamental complicating factors.

It is the purpose of this paper to discuss these adverse factors which have not been clearly understood. In this discussion emphasis will be placed primarily on analysis of the pathophysiology responsible for the difficulties encountered in the postoperative course. Related clinical, surgical, bacteriological, and therapeutic aspects of these problems will also be considered. It is hoped that definition and clarification of the complications which can occur in a post-operative mastoid cavity will help the surgeon in his responsibility for further reducing the number of cases which fail to heal in a reasonable period of time.

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† From the Lempert Institute of Otology, and Lempert Research Foundation, Inc.

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In attempting to explain the poor quality of healing which is sometimes encountered after temporal bone surgery, references have been made to such widely varying influences as the following:

A. *Local Factors.* In otology the surgeon deals with a wound which is a gross operative defect in bone. Unlike the general surgeon, concerned mostly with soft tissue wounds, he does not have the crucial advantage of being able to close his wounds primarily; furthermore, the blood supply, supporting healing processes in a bony cavity, is poor, and being exposed externally, the wound is subjected to lower temperatures which also delay healing. Undoubtedly, these local factors account for the fact that mastoid wounds heal more slowly; but they do not explain why, after the same operation, some ears heal in two or three months while others can continue to discharge indefinitely.

B. *Systemic Factors.* It has been shown that systemic factors have some effect on the progress of healing. Among these general factors are: age, disturbed water balance, abnormal metabolism, avitaminosis, protein deficiency, and anemia.[1] It is true that these factors theoretically and experimentally may be capable of delaying healing. It would probably be missing the problem entirely, though, to accept them as the basis for our difficulties in promoting dry ears. It is understandable how these systemic factors can play a part in delaying healing in individuals with debilitating diseases, severe burns, or states of long-standing malnutrition. It is difficult to believe, however, that such deficiencies can be present in healthy individuals undergoing elective surgery—individuals who reveal no abnormalities on routine preoperative physical and laboratory examinations; furthermore, observations of patients with chronic draining cavities reveal no difficulties in postoperative healing after undergoing surgery in other regions of the body.

C. *Technique of the Surgeon.* Until recent years, practically all of the surgery done on the temporal bone was for infection. When, after a radical mastoidectomy, for instance, a cavity continued to drain for a long period of time, it was assumed that incomplete removal of pathology was responsible for the persistent discharge. This attitude led to many articles in the

literature which advocated better surgery as the answer to the problem of obtaining dry, healed cavities. There can be no argument with this basic principle, for certainly if the surgery performed is not extensive or adequate enough to remove foci of infection within the temporal bone, it is unreasonable to expect a permanently dry ear. Today, however, a great many sterile temporal bones are operated upon in the interest of performing functional surgery. In these bones there is no infection to remove and consequently none to remain. Yet we are finding the same resistance to healing in some of these cavities that we have long seen following radical mastoid surgery. Today, also, with the availability of good lighting, magnification, and especially better teaching of surgical anatomy, there are many men who have perfected themselves in the technique of exenterating pathology anywhere in the temporal bone; yet they are discovering that surgical ability, as important as it is, does not necessarily assure dry postoperative cavities. It is becoming more and more evident that the advantage of good temporal bone surgery can be easily lost during the postoperative period where there are fundamental factors which can influence either prompt or delayed healing.

Before discussing these complications of healing it is in order that we first know what constitutes normal healing in a mastoid wound. We should have a working conception of those events of repair which take place in an uncomplicated cavity—one in which healing is occurring under the best possible conditions at the fastest possible rate.

II. THE UNCOMPLICATED CAVITY.

A mastoid wound heals by secondary repair. A substrata of granulation tissue must first develop over the osseous walls before epithelium can spread across the wound to cover the defect.

During the first three or four days following an operation there is an inflammatory reaction in the wound. This reaction elicits exudation of blood elements into the area, resulting in the formation of a coagulum (see Fig. 1) which covers and protects the wound surface. This coagulum, made up of fibrin and other elements of the blood, appears as a reddish, jelly-

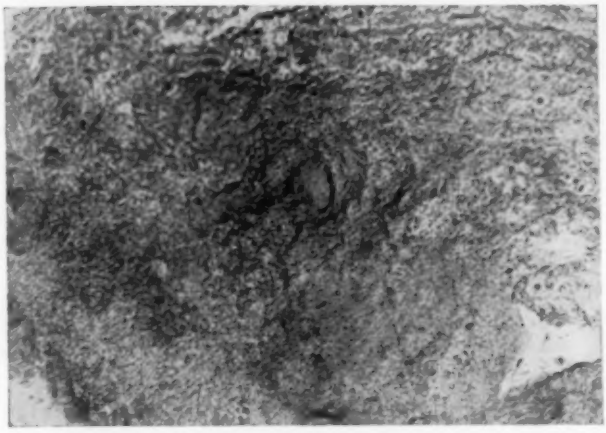

Fig. 1. Medium power (270X). Biopsy specimen of coagulum removed from fenestration cavity on tenth postoperative day.

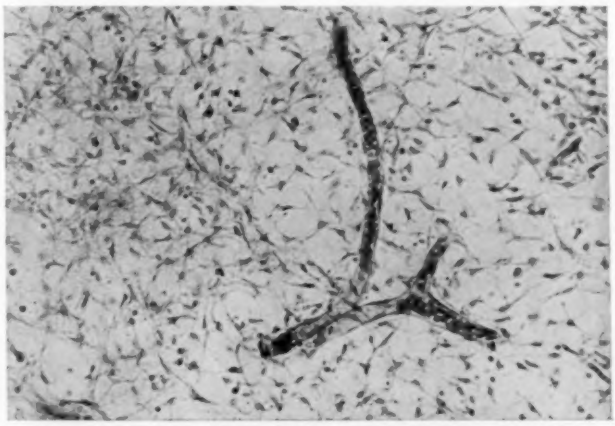

Fig. 2. Medium power (270X). Beginning formation of granulation tissue showing new blood vessels and a connective tissue network made up by the fusion of the thin branching processes of the fibroblasts. Clear intercellular spaces contain non-staining ground substance. (Histological section of mastoid cavity in monkey, twelve days after operation.)

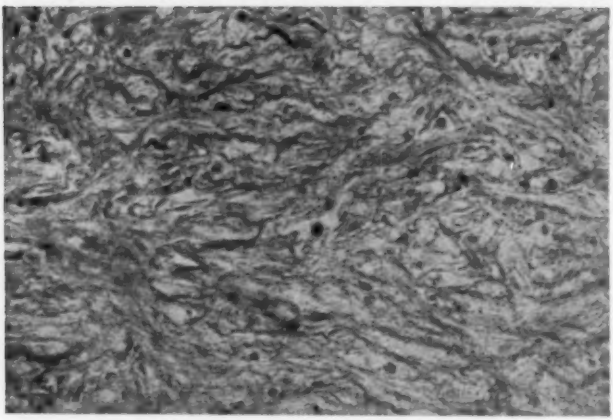

Fig. 3. High power (900X). Biopsy specimen of granulation tissue from fenestration cavity on 16th postoperative day, showing elaboration of connective tissue fibrils and elastic fibers. Note presence of macrophages and other cells forming a protective and scavenging system.

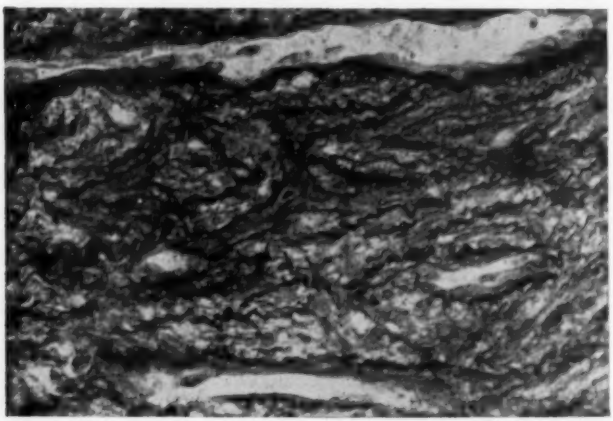

Fig. 4. High power (900X). Biopsy specimen from fenestration cavity on 21st postoperative day, showing well organized connective tissue.

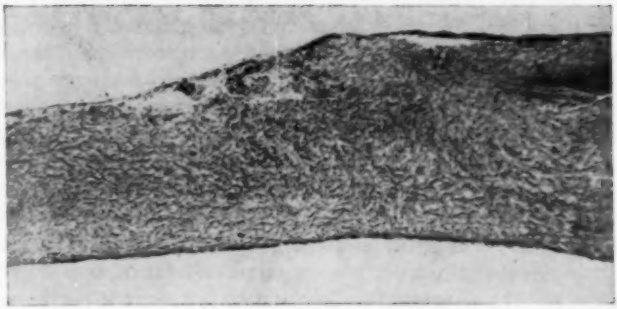

Fig. 5. Low power (80X). Biopsy specimen of granulation tissue removed from uninfected postoperative cavity on 30th postoperative day. Note smooth healthy surface receptive to the growth of epithelium.

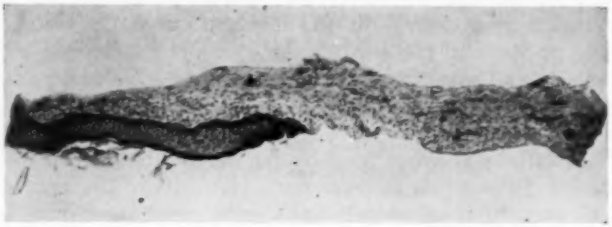

Fig. 6. Low power (80X). Biopsy specimen from 90-day postoperative fenestration cavity, showing epithelium growing over uninfected granulation tissue.

like exudate. In effect, it provides provisional closure of the wound and offers protection against drying and injury of the underlying structures.[2] Beneath its protective surface the activities of healing begin. These activities are concerned at first, for two or three days, with the removal of injured tissue cells through phagocytosis and enzymatic digestion.[2] Before this period is over regenerative activities have already begun.[3] These are characterized by the appearance of capillaries and fibroblasts which begin to form a sheet of young granulation tissue (see Fig. 2). The capillaries arise from endothelium of surviving capillaries[4,5] and the fibroblasts are either brought in with the blood elements or migrate from surviving connective tissue in the area.[6] The young granulation tissue, as it

develops, offers a better protection to the injured osseous walls than the jelly-like exudate[7] which now gradually disappears as its fibrinogen content decreases, and a resorption of the exudates takes place. By the end of the third or fourth postoperative week most of the exudates have been removed, and a thin sheet of granulation tissue, covering the walls of the cavity, has become well organized (see Fig. 4). It now consists of new capillaries and a connective tissue network, made up by the fusion of the thin branching processes of the fibroblasts (see Fig. 2). The intercellular spaces of the network contain an amorphous jelly known as ground substance (see Fig. 2). Angevine[8] has likened the situation to "absorbent cotton with the ground substance representing the interstices between the cotton fibers." This extremely interesting substance is present in varying amounts depending upon whether the tissue is young or old, suffers injury, or becomes infected. The fibroblasts are responsible for the elaboration of the connective tissue fibrils[9] and the elastic fibers[10] which become embedded in the ground substance (see Fig. 3). As the connective tissue matures the fine fibrils coalesce to form larger collagen fibers which, in turn, form sheets of collagen. The direction of the collagen fibers is determined by the lines of tension in the tissues.[11,12] In addition to these main elements of the connective tissue structure, other cells such as macrophages, mast cells, lymphoid cells, plasma cells, and eosinophils may be seen[13] (see Fig. 3). Tissue fluids, derived from the plasma, are also present.[14]

As long as the connective tissue remains uninjured and uninfected it offers a smooth, firm, receptive surface for the implantation of new epithelium (see Fig. 5). Epithelium begins to grow over the newly formed granulation tissue (see Fig. 6) by a process of cell division and migration from the wound edges and from any skin which may be present in the bowl of the cavity. Healing is accomplished only when a continuous layer of epithelium has covered the new granulation tissue. Following closure of the wound, cell division may continue after migration has ceased, adding thickness to the covering epithelium.[15]

Management of the Uncomplicated Cavity. Now, how should a cavity that is healing without complications be treated?

First of all, it should be realized that there is absolutely no evidence to support the multitude of claims that various substances applied to wounds stimulate healing.[1] Although wounds have engaged the attention of physicians for centuries, not one single method has been discovered for speeding up nature's timetable of healing beyond the optimal rate under ideal conditions.[16] As long as a cavity is healing without complications there is nothing a surgeon can do to improve on the biological processes taking place. The great temptation to treat a cavity, on the other hand, may result in a number of factors which interfere with the natural tendency for wounds to repair themselves. These effects, which may be brought about by manipulation in the cavity, are:

Removal of the Elements Needed for Healing. Cleaning a cavity, in the early stages of healing, only removes the exudates and the blood elements present, which nature put there in the first place, to accomplish the events of healing.

Trauma. After healthy granulation tissue has formed, wiping the cavity with a cotton-tipped applicator, except in the gentlest manner, causes traumatic inflammation and edema of the newly formed granulation tissue.

Infection. Unless manipulations in the cavity are carried out under strict aseptic techniques they may be responsible for innoculating the uncovered granulation tissue with bacteria. In some cases, insufflation of an unsterile powder may introduce more infection than it prevents.

Destruction of Tissue Cells. Some antiseptic agents applied to a wound may have destructive action on living tissue as well as on bacteria.[17]

Damage to New Epithelium. Soon after a cavity has become healed, new epithelium, which is at first more firmly adherent to the overlying scab than to the underlying connective tissue,[18] may be pulled away when the surgeon is too eager to remove crusts.

An uncomplicated cavity should be thought of in terms of biological and histological events and not in terms of mechanical cleanliness. It is becoming more and more obvious that a

good attitude to assume toward uncomplicated healing is one which might be called "judicious neglect."

III. THE COMPLICATED CAVITY.

There are four fundamental complicating factors which can delay permanent healing in a postoperative mastoid cavity. They are:

A. Bacterial infection.

B. Mycotic infection.

C. Cyst formation.

D. Cicatrization.

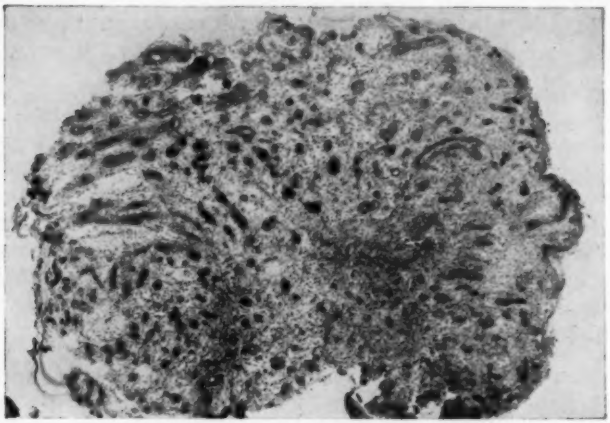

Fig. 7. Very low power (25X). Typical "humped up" infected granulation removed by curettage from a purulent cavity. Note marked accumulation of intercellular fluid, increased vascularity, and heavy infiltration of leucocytes.

I choose to call these fundamental factors because in all unhealed ears with long continued drainage, one or more of these four factors will be found responsible for the discharge. These are the patho-physiological complications which explain the tremendous variation in the healing properties of different cavities. They are factors which have great clinical impor-

tance, and over which the otologist has some measure of control.

A. *Bacterial Infection.*

By far the most frequent complication in the healing mastoid is bacterial infection. During the postoperative course many chances for contamination occur in a wound which requires two or three months for complete epithelization. It is not economically practical to keep a patient hospitalized until

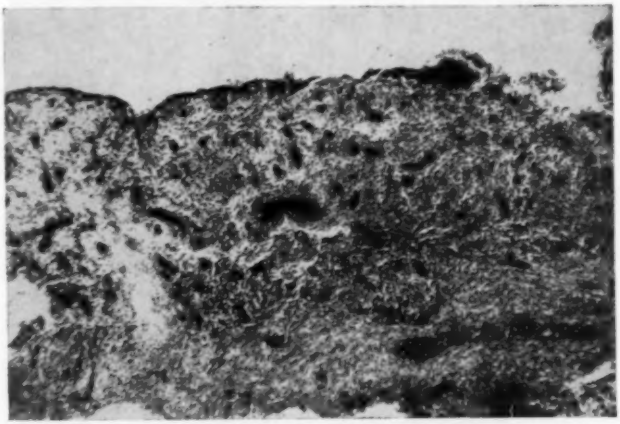

Fig. 8. Low power (80X). Biopsy specimen from cavity with infection for a period of ten months. Note increased vascularity, accumulation of intercellular fluid, and heavy infiltration of leucocytes in the superficial layer of infected granulation tissue. Collagen is building up in the deeper layer of connective tissue.

healing is complete, and patients refuse to wear a sterile bandage for long periods of time, calling attention to an operation involving a sense organ; furthermore, long term prophylaxis with antibiotics is neither wise nor safe.

Once infection has become established in a cavity, toxins are elaborated by the invading organisms. These toxins cause damage to the healthy granulation tissue.[1] The surface of the injured granulation tissue undergoes a commensurate protective response, to prevent spread of the infection to deeper areas. This response is characterized by several reactions:

Fig. 9. Low power (80X). Biopsy specimen from infected postoperative cavity showing arrest of healing. Epithelial growth (left), which has been extending over a healthy bed of connective tissue (bottom) ceases to grow further on meeting an area of infected granulation tissue (upper right). Epithelial cells pile up at the margins of the wound forming a thick border and further impeding growth of cells across the wound surface. Note exudate on surface of infected granulation tissue.

Increase in the Amount of Ground Substance (see Figs. 7, 8). This intercellular substance in general acts as a barrier against the spread of infection, and an increase in the amount present acts as a further protection.

Increased Vascularity (see Figs, 7, 8).

Influx of Leucocytes and Phagocytes (see Figs. 7, 8).

Active Exudation (see Fig. 9).

All of these activities are ideal responses for a defense against infection.[19] In principle, then, the edematous granulation tissue represents a barrier against bacterial invasion and toxin absorption.[7,17] Its protective presence accounts for the clinical fact that a postoperative cavity can drain pus for months or years without the patient's showing any systemic effects;[20] however, epithelium will not grow over such infected granulation tissue. Unless epithelial cells have healthy granulation tissue on which to implant themselves, the cells pile up at the margins of the wound, forming a thick border which further impedes the growth of cells across the wound surface[21] (see Fig. 9). As long as infection remains in the cavity growth of epithelium does not take place, and the progress of healing is arrested.

Infection should be prevented, of course, in so far as possible. It seems unnecessary to go into those details concerning the need for sterile precautions in the care of an open wound during postoperative dressings and office visits. Every surgeon should be aware that this is an important part of his responsibility. It is only realistic to understand, however, that in the activities of the patient there are many circumstances leading to infection which are beyond the surgeon's control. Anyone who does much temporal bone surgery must expect to contend with the problem of infected cavities.

Necessity for Removal of Infection to Reestablish the Progress of Healing.

After infection has occurred there is no longer any justification for maintaining an attitude of "judicious neglect". Active measures must be taken to eliminate this complication if

the progress of healing is to be reestablished. The cavity must be cleaned and the areas of pathology determined.

Mechanical measures, such as the common practice of curetting away the edematous granulation tissue, accomplishes little unless at the same time infection is eliminated. Without the elimination of infection, the toxins of bacteria still present, again injure the connective tissue on the surface of the curetted base, and within a short time granulations reappear in the same area. This cycle, with curettement and reappearance of infected granulation tissue, can go on indefinitely as long as suppuration remains in the cavity.

The Problem of Eliminating Postoperative Mastoid Infection.

This problem is related to: *1.* the types of bacteria present, *2.* the resistance of these bacteria to therapy, and *3.* the difficulties of delivering sufficient concentrations of a drug to the site of infection.

1. *Types of Bacteria Present in Postoperative Mastoid Cavities.*

In order to satisfy myself as to the general distribution of bacteria found in infected postoperative mastoid cavities, I collected and studied a series of cultures from consecutive patients being seen in the course of routine postoperative office care. These were cultured aerobically and anerobically. Dr. Philip Meltzer[22] has made a similar study at the Massachusetts Eye and Ear Infirmary. In summary, both these studies showed that approximately 50 to 60 per cent of organisms cultured were staphylococcus aureus, coagulase positive. The large majority of the remaining organisms were of the pseudomonas or proteus types.

These organisms, with others such as fungi and E. coli, are bacteria which seem to be present fairly consistently in the normal flora of the skin.[23,24,25] Finding them in mastoid wounds simply reflects the opportunities for contamination from the skin of the patient or the hands of medical personnel treating the ear.

2. *Resistance of These Bacteria to Therapy.*

A further explanation for their presence, consistently, in mastoid wounds is that these are the bacteria which develop as superimposed infections in wounds in general, as a result of antibiotic suppression of more drug-sensitive microorganisms. As Cannon[26] has pointed out, one of the complications of greatest current interest is the increasing frequency with which we are being confronted with infections attributable to staphylococci, pseudomonas aeruginosa, and proteus, all resistant to most of the antibiotics now in use.

3. *Difficulties of Delivering Sufficient Concentrations of Therapeutic Agents to the Site of Infection.*

It is generally recognized that there are few instances of infection in the body which cannot be more effectively reached by way of the blood stream than by locally applied agents.[27] When a mastoid wound grows older, however, and has been the site of infection for a long period of time, it develops characteristics which limit the effectiveness of systemically administered agents. Where healing has been slow, scar tissue formation takes place in the deeper layers of connective tissue (see Fig. 8). This deeper connective tissue becomes thickened, sclerotic, and poorly vascularized, and blood-borne drugs reach the surface layer of infected granulation tissue in poor concentrations.[28] MacLeod[29] has stated that such an area of infection becomes "essentially walled-off from the general circulation." I have seen this confirmed clinically many times, as evidenced by the inability of parenterally administered antibiotics to control infection in old postoperative mastoid cavities although present in inhibitory concentrations in the blood.

Rationale of Therapy. There is a solution to this problem of overcoming drug-resistant types in an area of infection surrounded by a fibrous barrier. This calls for a design of treatment which will deliver a wide-spectrum antibiotic to the site of infection in such form that it will remain there a sufficient length of time to accomplish maximal exposure of the organism to the drug. As Davis and McDermott[30] have pointed out, susceptibility of an organism to a chemotherapeutic agent is a quantitative rather than a qualitative attribute; therefore, if a chemotherapeutic agent is rendered at a high enough con-

centration, it can inhibit practically all strains of bacteria. In other words, if we can deliver a sufficently high concentration of an antibiotic at the site of infection, we can get not only wide antibacterial activity but also activity even against organisms which are not usually susceptible to lesser concentrations of the same drug, and we can overcome drug resistant types.

Delivering high concentrations of a blood-borne drug to the site of a chronic infection in the postoperative mastoid cavity is difficult, however, not only because of the presence of the fibrous barrier surrounding the site of infection, but also because of the danger of potential systemic toxicity; therefore, local therapy becomes the route of choice in old suppurative mastoid cavities.

In general, however, the common fault of local therapy is that it is carried out in concentrations which are too weak. As Bunn[21] has stated, success in the management of any infection depends upon exposing the organism to sufficient concentrations of its antagonist. Where the infection is due to drug-resistant bacteria, higher concentrations of a drug must be used. A criticism of most of the commercially available agents for local therapy is that they are supplied in strengths that will meet the demands of a wide market. For instance, otic drops are supplied in strengths of one-half to one per cent; ointments in strengths of 3-5 mg./Gm. Obtaining sufficient concentrations of an antibiotic at a particular site of infection for any length of time is, therefore, difficult. Effective concentrations, sufficient to end an infection rapidly even in the presence of drug-resistant organisms, can be produced best by introducing an antibiotic in the form of a concentrated powder, delivering to the site of the infection as much as 250-500 mg. of a drug.

Management of the Cavity Complicated by Bacterial Infection. The approach to sterilizing suppurative cavities is illustrated in the following clinical experience, which is presented, not as justification for choosing a specific agent, but rather as an explanation of the preceding rationale of therapy.

About five years ago, after running sensitivity tests on a series of cultures collected consecutively from infected post-

operative fenestration cavities seen in routine office practice, I selected chloramphenicol for a long-term clinical trial because of its broad antibacterial spectrum and its effectiveness against proteus, pseudomonas aeruginosa, and resistant staphylococci. Since then I have used it in 657 cases of postoperative suppurative fenestration and radical mastoid cavities in which the infection was not previously controlled by less effective routine measures. Treatment is carried out in the following manner:

"Infected granulations, which are "humped up" and interfere with the contour of the cavity, are removed by curettage and the denuded area dried with cotton packs moistened with adrenalin. The powder from a 250 mg. capsule of chloramphenicol is then dropped into an ear speculum and worked into the cavity to the unepithelized area or areas with a cotton-tipped probe. Care is taken to see that all unepithelized areas are thickly covered with the powder, since infection in the entire cavity must be eliminated at one time to prevent foci of infection from remaining. For instance, patients with denuded areas on the tegmen must be placed in such position for treatment that the powder may be transferred from the speculum to this area. Two capsules (500 mg.) may be used if the denuded area is extensive. The powder mixes with secretions and soon becomes a caked paste which, in two or three days, becomes a dried crust. Epithelization of the sterilized area takes place beneath the crust. One or two treatments, one month apart, are usually sufficient to render a cavity aseptic. It is unnecessary to see the patient frequently. As a matter of fact, once the cavity is dry, the crust should not be disturbed for a month or six weeks, since lifting up the crust will pull away the new epithelial tongues which are at first more firmly adherent to the crust than to the underlying connective tissue.[18] Success with this method of treatment has been surprisingly consistent, not only in infections with the Gram-negative group, but also in wounds infected with Gram-positive organisms."

In 657 cases of persistent discharge treated, 538 (82 per cent) cavities became dry and completely epidermized after the following number of treatments:

No. of Treatments	No. of Cases	Percentages
1	310	57
2	154	29
3	53	10
4	16	3
5	3	.5
6	2	.5
	538	100.0

In the remaining 119 cases (18 per cent) the treatment was not carried to successful completion because of: *1.* development of reactions; *2.* cessation of treatment due to the fear of reactions; *3.* association of the infection with other complications in the same cavity (cysts, fungus); *4.* cases which could not be followed, and *5.* failures.

Sensitivity of the patient to chloramphenicol developed in 36 (5.5 per cent) of the 657 cases treated. This reaction to the use of chloramphenicol in heavy concentrations was no greater, in my experience, than that encountered when weak solutions of drops were used. Sensitivity developed on a quantitative basis, 70 per cent occurring in cases where the drug was used more than three times. This small percentage of reactions can be further reduced if the clinician will realize that he has a remarkable instrument for rendering a cavity aseptic but will not prolong treatment if the infection does not readily respond. (There is very little to be gained by prolonging the treatment in any event. It is significant that 517 (96 per cent) of the 538 cases successfully treated required no more than three treatments.)

The possibility of sensitization with the use of chloramphenicol cautions against the indiscriminate use of this antibiotic. This disadvantage prevents its becoming what might be an ideal agent for our purposes. We do not yet have an ideal antibiotic for local use, one which could be easily introduced into a cavity, in such form that it would remain active in the infected area for a long period of time, in sufficient strength to be effective over a wide range of bacteria, without sensitizing the tissues.*

* Reports on newer antibiotics appearing all the time make any estimate of this situation unpredictable. A recent report[32] cites the use of erythromycin and oxytetracycline in pyrogenic infections of the skin without any evidence of sensitivity.

Other forms of antibacterial treatment, which do not involve the small calculated risk of sensitivity, are preferable in early postoperative cases or may be necessary in instances where sensitivity has already been encountered in old chronic draining cavities. When the identity of the infecting organism is known to be staphylococcus, large concentrations of bacitracin powder may be tried. Sensitivity to this agent, when used locally, is practically unknown. Aerosporin may be used in the same way, without risk of a sensitizing effect, when the infecting organism is known to be pseudomonas aeruginosa. Other treatments, eliminating the possibility of sensitizing effects, consist of the use of various ointment-combinations of bacitracin, polymyxin, and neomycin. In general, these preparations, in standard forms, are less effective against postoperative mastoid infections because of their weak concentrations. Results, however, are enhanced when quarter-inch packing is impregnated with these ointments, and the cavity is firmly packed. Twyman[33] 33 years ago showed that epithelium will continue to grow when subjected to the same pressure which collapses the capillaries in granulation tissue and thereby suppresses its growth.

B. *Mycotic Infection.*

Another complicating factor which can delay healing in a postoperative mastoid cavity is mycotic infection which flourishes in a bacteria-free field, and is more prone to appear in cavities after effective antibacterial treatment has been carried out. Aspergillus, as well as some other molds (Penicillium and Mucor species) are responsible for stubborn, chronic infections in postoperative wounds. Practically, however, the problem may be narrowed to Aspergillus niger in particular. In my experience, this has been by far the most frequent type of mycotic infection encountered in postoperative cavities. When this contaminant occurs it is obvious that it must be differentiated from a bacterial infection, since no amount of antibacterial therapy will affect the situation. Clinically it is easily recognized by the presence of a material resembling moist gray blotting paper, on the surface of which may be seen the black spore heads so characteristic of this type of fungus. The patient complains at first of intense itching, followed by dis-

charge and pain. When cleaned the cavity has a degree of inflammatory reaction paralleling the duration of the infection.

Management of the Cavity Complicated by Mycotic Infection.

In my own experience, treatment of fungus infections in postoperative cavities, once very difficult, has ceased to be a problem since I began using an iodine compound, Vioform cream (3 per cent). This appears to be an ideal agent in these infections. I have now used it in 93 cases, without failure to eliminate fungus infection readily and easily, and without discomfort to the patient.

It is used in the following manner: All debris and membranes are first removed by mechanical cleansing. The cream is introduced into the cavity with a syringe to which is attached a piece of flexible plastic tubing. It is then worked into all recessed areas with a cotton-tipped applicator. This is followed by filling the entire cavity (leaving the fenestra clear, in fenestration cavities). One treatment usually soothes the inflammatory reaction of the tissues and eliminates the fungus. An additional one or two treatments are given one week apart to insure against return of the infection.

C. *Cyst Formation.*

A third complication that can occur to prevent permanent healing of a postoperative cavity is cyst formation (see Fig. 10). This results in a type of discharge which, unlike the preceding complications, is not caused by an invading organism, but is caused by a secreting epithelium, either squamous, cuboidal, or columnar.* Consequently, recognition of this type of drainage becomes essential to insure proper treatment. The discharge has a characteristic mucoid appearance, and is tenacious and stringy. As one removes it from the ear it has the appearance and consistency of egg albumin. Some cysts will be found filled with a chocolate-colored hemorrhagic fluid. These cysts form most frequently in the sino-dural angle or in

* I have biopsied one cyst from a mastoid cavity which contained no epithelial lining at all, the cavity being surrounded by fibrous tissue. This finding may be explained by the effect of increasing pressure of the cyst contents on the epithelium until it becomes atrophic and disappears entirely.[24] The presence or absence of an epithelial lining in a cyst also explains why some cysts continue to enlarge and rupture, while others do not.

the mastoid tip. Skin over the cyst appears bluish, indicating a mucus-filled space beneath. They may appear months or even years after operation, more often after the cavity has been dry for a long time. The clinical course is usually one of alternating periods of mucoid discharge with periods when the ear is dry. When a cyst is small, and located in such a position in the cavity that it cannot be visualized, the nature of the discharge may not be readily determined, especially if there is superimposed suppuration.

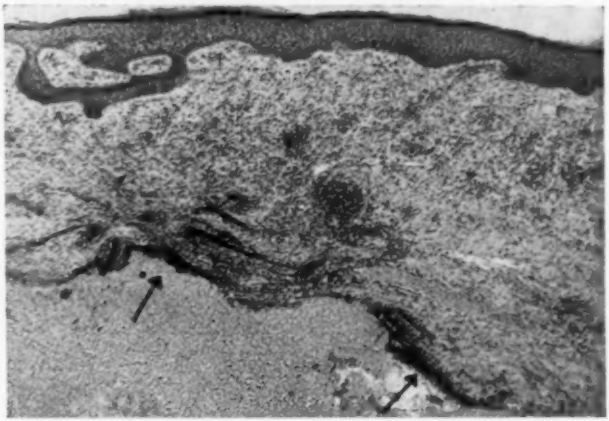

Fig. 10. Low power (55X). Biopsy specimen from fenestration cavity containing a cyst seven years after operation. The cyst cavity, filled with cystic material, is at lower left. Arrows indicate cystic lining.

The etiology of these cysts has been puzzling. One explanation is that they are retention cysts, formed during the process of healing when epithelium covers over a mastoid cell containing mucous membrane. If this were the etiology, it seems unlikely that any cavity could heal without subepithelial cyst formation, since there are always some cells left somewhere in a postoperative cavity. A more likely explanation is that cysts are the result of atypical epithelial growths. Arey[35] believes that cyst formation may occur in granulating wounds which have been injured. In other words, in a cavity which has been the site of infection or much trauma, the connective

tissue may become subnormal. Epithelial processes may extend downward into this injured connective tissue, forming an atypical growth, or as Arey has stated,[35] "can invade growing connective tissue such as is active in filling a defect."

Whatever the etiology, the fact that active, secreting, subepithelial cysts can occur in postoperative cavities is a reality. Such cysts will usually rupture when they become distended, furnishing the source of a persistent or intermittent discharge; at other times they may fail to rupture, causing pressure dissection instead. This can result in lifting up a considerable area of skin from the osseous wall causing pain, symptoms of pressure, and in the fenestration cavity, dizziness.

Management of the Cavity Complicated by Cyst Formation.

In the observation of approximately 2000 postoperative fenestration and radical mastoid cavities during the past five years I have encountered 52 cysts requiring treatment (approximately 2.5 per cent).

No amount of antibacterial treatment has any effect on cystic drainage. The cystic membrane must be eliminated. Although surgical intervention in the cavity makes complete removal easier, the patient can usually be spared an operative procedure. In the majority of cases, destruction of the cystic epithelium may be accomplished as an office procedure in the following manner: As much as possible of the presenting face of the cyst wall is removed with cutting or biting instruments. The remainder of the cyst cavity is then packed, with narrow iodoform gauze weekly, for two or three weeks. This keeps the lumen of the cyst open, converts it to a part of the cavity lining, and destroys the secreting epithelium. A dry cavity then becomes possible unless there is a superimposed purulent discharge present, in which case antibacterial therapy must also be carried out to obtain epithelization of the destroyed cystic area.

D. *Cicatrization.*

When a mastoid cavity has been the site of long delayed healing, a fourth factor comes into play, which makes it more difficult to obtain *permanent* healing. This factor is excessive cicatrization. Cicatrization is essentially the conversion of

granulation tissue into scar tissue. When chronic infection persists for a long period of time there is repeated damage to the granulation tissue by toxins of bacterial organisms present. This leads to repeated episodes of necrosis in the tissues. More and more fibrous tissue reaction follows, and in the course of time an increasing amount of scar tissue forms. This is the most characteristic feature of chronic inflammation.[36] As the scar tissue undergoes shrinkage, capillaries re-

Fig. 11. Low power (80X). Biopsy specimen from fenestration cavity seven years after operation, showing poor quality of epithelium over sclerotic connective tissue. Note absence of rete pegs and thin, flat atrophic nature of epithelium.

gress, and vascularity decreases. Such scar tissue supports a poor quality of epithelium. It is thin, flat, and atrophic (see Fig. 11), and is easily wiped away because it does not have rete pegs attaching it firmly to the connective tissue.[37]

Management of the Cavity With Excessive Cicatricial Healing. In the cavity where healing has been prolonged one should be aware of this histological situation. Extreme gentleness is necessary in removing crusts from the dry ear, or in periodically removing accumulated wax, in order to prevent traumatization of the epithelium. Rough cleaning of the cavity can

wipe away the epithelium, leaving a denuded area which may become infected and reestablish a discharge.

IV. REMARKS ON SURGICAL TECHNIQUE.

A. *Need for an Adequate Opening to the Cavity.*

An adequate opening is obviously essential if the otologist is to exert any measure of control over complications which may take place during the events of healing. Failure to provide for it at operation is often responsible for complete defeat in efforts to obtain a healed, dry cavity. Nothing is so frustrating or so difficult as trying to carry out instrumentation, or trying to apply medication to a cavity blindly, through a small constricted opening. The principal factor in atresia of endaural openings is a prominent inferior spine (the spine existing between the external auditory canal and the exenterated mastoid after the posterior bony canal wall has been removed). The upper circumference of endaural openings, no matter how extensive the incisions, will heal more or less at the same level because of the conformity of the cartilagenous components of the auricle to fixed positions. Consequently room for an adequate opening must be provided by removing bone inferiorly, which should include not only the inferior spine but also a lowering of the floor of the external auditory canal. Adequate diameter of the opening in an antero-posterior direction may be assured by removing a small semilunar piece of cartilage from the anterior edge of the conchal cartilage. With the routine postoperative use of antibiotics the threat of perichondritis with this procedure is minimal.

B. *Size of the Cavity.*

Emphasis on the reasoning that a limited cavity* assures more rapid healing because there is less surface area to be epithelized, has been out of proportion to its importance. We know, on the one hand, that regenerating epithelium extends faster in smooth and shallow wounds than in uneven wounds, or where there are mechanical obstacles to the movement of cells.[38] For this reason it follows logically that the limited cavity with smooth surfaces favors healing. This favorable factor

* The term *limited cavity* is used here in the sense that cells posterior to the sinus plate and cells below the level of the floor of the external auditory canal are not removed.

for the spread of epithelium pertains, however, only as long as the healing remains uncomplicated. The introduction of infection affecting the surface layer of granulation tissue, for instance, can delay and arrest healing in a small or a large cavity; and it is one of the fundamental factors such as this which is usually responsible for long-delayed healing—not the difference in the amount of surface area to be covered by epithelium.

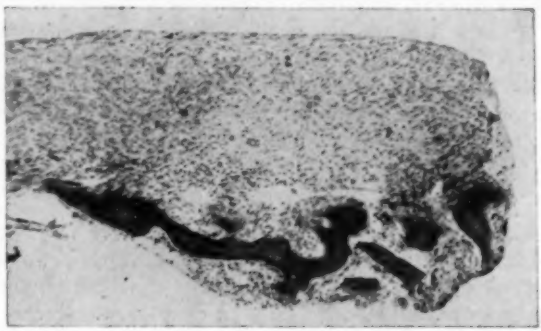

Fig. 12. Low power (80X). Biopsy specimen from fenestration cavity showing how small cellular defects in the osseous wall of the cavity are filled in with granulation tissue.

What is of more importance is that a limited cavity is easier to take care of postoperatively because all surfaces are more easily visualized. In the event that complications develop they can be observed and properly treated.* A large cavity, on the other hand, may even be difficult to take care of routinely. When complications appear, one may be defeated in his efforts to obtain a dry ear because he is not only unable to visualize the pathology but is also unable to apply medication to recessed areas, unless a very large endaural opening has been provided for at operation.

* It has been suggested that retained cells in a cavity following fenestration may become the site of a postoperative mastoiditis. Like Day[19] I have had no such experience, nor have I ever found it necessary to revise a cavity because of infected cells in order to get a dry ear. Granulation tissue fills in small defects (see Fig. 12) and the overlying bed of granulation tissue acts as a barrier to infection to protect underlying osseous structures.

There is another side to the question. It is not always wise and it is not always easy to limit the size of a cavity. In doing a radical mastoidectomy, where there is chronic mastoiditis, the amount of bone removed must be governed by the extent of the infection. In the performance of the fenestration procedure one encounters all types of cellular development. In a large pneumatic or pneumosclerotic bone it is sometimes very difficult to limit the size of the cavity. without leaving large open cells. The resulting irregularities of the cavity wall, too large to be filled in completely with granulation tissue, may predispose to cyst formation by causing atypical sac-like epithelial growths. When one cannot do a *good incomplete* exenteration without leaving large open cells he should always do a *good complete* exenteration. In such cases it is necessary to exenterate all the cells, including retrosinus and tip cells, before smooth limits of the cavity can be obtained.

C. *The Role of the Skin Graft.*

If healing is attained when a wound surface is completely covered with epithelium then, at least from the theoretical point of view, it would seem that skin grafting should long since have solved all the problems of postoperative care. That it has by no means accomplished this is indicated by the indifference toward its use which still exists today, many years after introduction of this technique for decreasing the difficulties of postoperative care. Among otologists with whom I have discussed this question it is surprising to find how many have given up this procedure after having employed it at one time or another. This attitude is difficult to understand, in view of the number of recent reports in the literature, by some otologists, indicating increasing success and enthusiasm for skin grafting following temporal bone surgery.

It has been pointed out recently by Campbell[40] that the chief cause of failure with skin grafting in mastoid cavities has been the lack of care and time taken in obtaining and placing the grafts. On the other hand, those surgeons who have abandoned skin grafting, after a period of trial, usually explain that a reasonable measure of the success of skin grafting is whether or not a dry cavity is obtained in a shorter period of time and that since the postoperative course is not noticeably

different in enough cases to warrant the added trouble of this procedure, they have given it up.

It is not to be doubted that skill and careful attention is necessary in obtaining the grafts and applying them in intimate contact with all the contours and recesses of a cavity. I am far from convinced, however, that the ultimate fate of the grafts rests entirely on the skillful technique of the surgeon, or that ability in this procedure varies so considerably among a number of highly experienced otologists.

I believe that the real fundamental factors, one leading to the other, which are responsible for reducing the practical results of such a theoretically sound procedure as skin grafting are: *1.* the difficulties of getting a "take" of skin grafts to bone, and *2.* the hazards of infection to which the postoperative cavity is exposed at any time between operation and the complete epidermization of the wound surface. The most skillfully obtained and applied skin graft is still subject to the hazards of poor blood supply from bone, unfavorable pressures by packing, serum dissection, shrinkage, and, in radical cavities, sloughs due to infection. The net result of the amount of skin which "takes" in the usual so-called completely grafted cavity is considerably less than 100 per cent. This leaves bare areas of bone in the postoperative cavity which must be healed by the same process necessary in ungrafted cavities—first by the formation of a substratum of granulation tissue, followed by the slow growth of epithelium from adjacent skin margins over the unepidermized area. Thus, as in the ungrafted cavity, for a period of time after operation, there is uncovered granulation tissue which is vulnerable to infection. When infection does occur, delay and arrest of healing can take place to the same extent as in the ungrafted cavity. It must be remembered that a cavity does not become healed and dry until complete epidermization has occurred, and that a small area of infected granulation tissue can keep a cavity draining for as long a period of time as a large area. The problem is the same. Infection must be eliminated before healing takes place. It is true that if infection does not intervene, grafted cavities have the advantage of healing faster than ungrafted cavities. Under the same circumstances, however, a cavity without free grafts heals fast enough not to present a problem.

Usefulness of free grafting in mastoid cavities is probably better illustrated by other more fundamental advantages. Even if the "take" of skin is only partial and infection does occur in the cavity, scattered areas of grafted skin play an important role in preventing the cavity from filling in with fibrous tissue. In an infected cavity where there is no skin, there is a tendency on the part of nature to heal the wound defect by second intention. It has probably been the experience of every otologist, at one time or another following a radical mastoidectomy, to observe a cavity containing no skin fill in with fibrous tissue despite all his efforts to prevent it, and finally to close off at the very surface of the wound margins. This is brought about by the fact that pus is more detrimental to the growth of epithelium than to the growth of connective tissue.[41] The growth of epithelium, arrested by the presence of suppuration in the wound, does not bridge across the cavity until it has filled in with connective tissue giving the epithelium the advantage of a more exteriorized environment where it is less affected by the presence of suppuration.

Another valuable advantage of grafting is that the Eustachian tube orifice may be sealed off in a radical mastoidectomy by grafting over the orifice. This is essential to prevent repeated discharge in the cavity with each upper respiratory infection, the occurrence of which makes it difficult to obtain a permanently dry cavity. A skin grafted cavity also results in less scar tissue beneath the epithelium overlying the areas of successful "take".[42] The advantages of this are discussed in the following section.

The use of local antibiotics in combination with surgical packing, as well as during the postoperative course, has undoubtedly been responsible for reports of increasing success with skin grafting. It should not be overlooked, however, that the local use of antibiotics has also been an enormous advantage in obtaining dry, healed cavities, without free grafts.

V. REMARKS ON THE HEALED CAVITY.

A cavity may be considered as healed when the connective tissue is completely covered by a continuous layer of epithelium. The processes of healing, however, do not stop at this

stage, but continue for many months thereafter,[43] consisting of maturing changes in the connective tissue. These maturing changes are brought about by a reduction in the amount of intercellular fluid, and a decrease in the number of cells and blood vessels. The protective reactions of increased intercellular fluid, increased vascularity, leucocytosis, and phagocytosis (see Figs, 7, 8) were needed in the uncovered granulation tissue as a barrier against infection. After epithelization provides protection to the connective tissue, these defensive reactions are no longer needed and gradually disappear. The result is a change of the granulation tissue to scar tissue. Capillaries regress, the intercellular fluid diminishes, and the loosely arranged fibrils and collagen fibers consolidate into thicker and more closely packed collagen bundles. Clinically, after epithelization, we can follow this change by observing the thicker, pink (but dry) soft tissue of the cavity gradually take on a thinner pearly-white appearance after a few months.*

These maturing changes, which take place as a natural course of events in all connective tissue contributing to the processes of healing, have little clinical significance when the healing has been uncomplicated, with deposition of connective tissue limited to the amount consistent with repair; however, when there has been a long delay in healing due to chronic infection, repeated damage to the granulation tissue stimulates the formation of more and more granulation tissue which gives rise, under pathological conditions, to collagen[44] in the deeper layers of connective tissue (see Fig. 8).

As Converse[42] has stated, "As the unhealed wound grows older this deep layer of fibrous tissue tends to increase at the expense of the superficial layer of granulations." The clinical effects of this thicker layer of connective tissue, covering the walls of the cavity, remain unnoticeable before complete epithelization has occurred. This is because the protective presence of large amounts of intercellular fluid, in the presence of an inflammatory stimulus, keeps the tissue loose and elastic (see Figs. 13, 14); however, after complete epithelization of

* In the occasional healed fenestration cavity the fenestra may be seen through the overlying skin almost as easily as looking through cellophane. This is accounted for by the fact that the disappearance of cells, fluid, and blood vessels leaves a more homogeneous tissue (made up almost entirely of a thin layer of collagen). Light striking the tissue is not refracted by several elements of different densities and is more readily transmitted.

the cavity there is a marked decrease in the amount of intercellular fluid in the tissues which leads to consolidation of fibrils and previously formed collagen into tightly packed collagen bundles (see Fig. 15). As this shrinkage takes place the result is a thicker, more sclerotic base of scar tissue underlying the epithelium. It is firmer, stiffer, and less elastic[45] than connective tissue found in cavities with uncomplicated healing. In addition to this early direct effect of the disappearance of intercellular fluid, there is a final progressive secondary con-

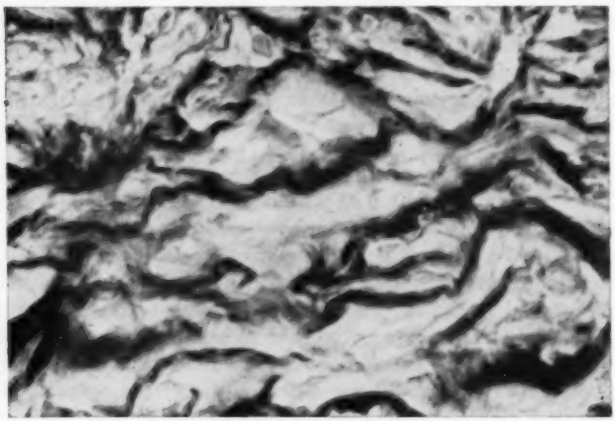

Fig. 13. High power (900X). Biopsy specimen from unepithelized fenestration cavity showing consolidation of connective tissue fibrils into wavy collagen bundles. This intermediate stage shows both fibrils and collagen bundles with a loose irregular arrangement and much intercellular fluid.

tracture of the connective tissue, which is a well-known characteristic of scar tissue, occurring several months to a year or so after a cavity has become epithelized.

In a cavity which has been the site of prolonged infection, these pathophysiological developments in the connective tissue can lead to two interesting effects:

A. *Reflex Sympathetic Neuralgia.*

In my observation of some 2,000 postoperative fenestration and radical cavities I have found the usual postoperative course

free from association with abnormal complaints on the part of the patients. Occasionally, however, a patient complains of a diffuse pain pattern on the operative side which may involve a spread of referred pain, with relative predominance of any or all of the following regions: the base of the neck, the suboccipital region, the mastoid process, the ear, the parietal region, the temple, back of the eye, and the face. The pain may

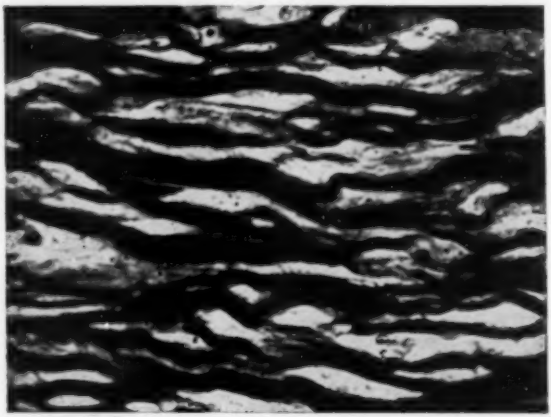

Fig. 14. High power (900X). Biopsy specimen from unepithelized fenestration cavity showing more advanced stage of collagen formation with orderly horizontal arrangement of collagen bundles. The tissue remains loosely arranged, due to the presence of large amounts of intercellular fluid.

be burning or lancinating in character, but usually is a dull, aching, or throbbing pain. It is often described as "headache." It may be intermittent or continuous. It does not coincide with peripheral nerve distribution. A few of these patients may complain of mild flushing of the face on the operative side, while others feel that the skin is cool and moist. Blurred vision is sometimes a symptom. These complaints are presented almost entirely by those patients whose ears have become dry after long-delayed healing due to infection. Patients almost never complain of these symptoms of referred pain before the cavity has become epidermized. Symptoms may continue for variable periods of a few months to a year or so after epithe-

lization and then gradually disappear. The syndrome may be abolished at any time if the epithelium breaks down and infection is reestablished in the cavity.

Among the extensive observations by Travell[46] on skeletal muscle pain and the trigger mechanism, she has described an almost identical composite pattern of pain, with concomitant autonomic effects, in a series of patients in whom a clinically related trigger area could be demonstrated in the sternomastoid muscle. The pattern of referred pain from the trigger

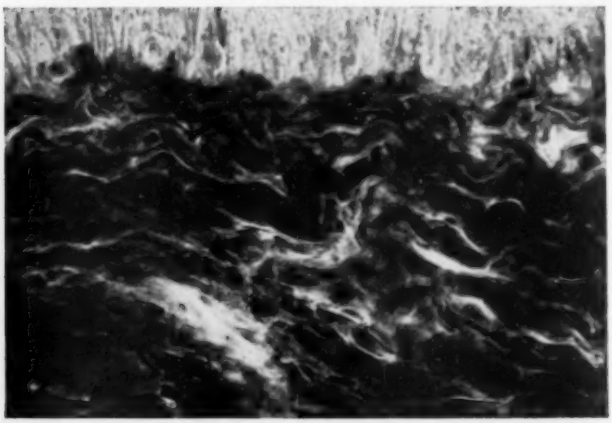

Fig. 15. High power (900X). Biopsy specimen from completely epithelized fenestration cavity showing tightly arranged collagen bundles after the disappearance of intercellular fluid.

area is essentially the same from person to person. Predisposing conditions leading to establishment of the trigger area were some form of trauma to the muscle, physical, infectious, thermal, or metabolic. Inserting a needle into the trigger areas gives rise to the characteristic pattern of referred pain. Infiltrating the trigger area with procaine abolishes the pain in the reference area.

Another pain syndrome, established as a result of injury and involving sympathetic effects, has recently been described by Casten and Betcher.[47] They have termed the condition "Re-

flex Sympathetic Dystrophy" and defined it as "an excessive or abnormal response of an extremity to injury." It is characterized by *1.* excessive and prolonged diffuse pain of varying intensity, seldom limited to a definite nerve distribution; *2.* vasomotor disturbances of the skin, either slight or severe, and consisting of either constriction or vasodilation; *3.* delayed functional recovery, and *4.* atrophic changes. Recommended treatment is interruption of the sympathetic outflow to the extremity, either by continuous procaine ganglion block or by surgical ganglionectomy.

The mechanism of referred pain is not well understood. A consensus of opinion on the subject would seem to be that there is a feedback circuit, possibly following sympathetic pathways along the blood vessels from an established trigger area, through the central nervous system, to the area of referred pain. This feedback mechanism is set off by stimulation of the trigger area and is maintained by the establishment of some hypersensitive state in the sympathetic arcs, causing a continuous discharge of impulses and a constant pain cycle.

In speculating on the mechanism of referred pain in the occasional patient following ear surgery, it seems evident that there is a definite autonomic relationship. Vasoconstriction and vasodilation of the vessels of the face, intermittent blurred vision, the failure of the pain pattern to correspond to somatic peripheral nerve distribution, and the aggravation of symptoms by fatigue and emotional stress tend to confirm it.

The establishment of a trigger area in the cavity also appears logical. A possible explanation is that in those patients where healing in the cavity has been long delayed due to infection, there is repeated injury to the granulation tissue resulting in a greater amount of scar tissue. When the scar tissue undergoes a shrinkage, a trigger area may be established as a result of stretching sympathetic fibers along remaining vessels in the area. The effect of eliciting referred pain by stretching the autonomics is well known. The impression of this pathophysiological explanation for the trigger mechanism is heightened by the observations that the persistence of symptoms of referred pain parallel the period of maturation and contracture in the scar tissue and usually disappear when this

period is ended, presumably with the ingrowth of elastic fibers and gradual resolution of the cicatricial nature of the tissue. At any time during the period of contracture of the scar tissue, if the epithelium in the new cavity breaks down, with reappearance of infection and reestablishment of increased intercellular fluid which renders the connective tissue more elastic, the symptoms of referred pain disappear; furthermore, in patients who have never complained of postoperative referred pain, but who develop a cyst in the cavity, with related stretching of the skin and underlying connective tissue, the same pattern of referred pain will often appear, persisting until the cyst is opened and pressure relieved.

B. *Auditory Changes Due to Cicatrization.*

It has long been observed that patients with chronic adhesive deafness have better hearing when the ear is discharging than when it is dry. In the presence of a discharge the connective tissue adhesions are soft and have greater elasticity. When the ear becomes dry these adhesions lose intercellular fluid, undergo contracture, and become tight and stiff, resulting in restricted movement of the ossicles.

Some variations in hearing observed after fenestration operations have been difficult to understand. Explanations probably are to be found in the pathophysiological changes which take place in the connective tissue. It has been observed that the highest hearing level, following a successful fenestration, usually is present when the cavity is in the early stages of healing. During this period the pedicle flap over the fenestra is still relatively thick but very sensitive to sound impulses because there is a large amount of intercellular fluid in the tissues. It is surrounded in the cavity by newly formed, loosely connective tissue (see Fig. 4). If healing takes place without infection, the connective tissue around the pedicle flap remains thin, and the effects of contracture are small. There is only a very slight drop from the maximum hearing level after epithelization takes place. This is due to a reduction of intercellular fluid incident to normal maturation changes taking place in all healing connective tissue. On the other hand, where long-standing infection occurs in the cavity, there is greater deposition of collagen in the deeper layers of connective tissue (see

Fig. 14). When healing finally occurs, a thicker, more sclerotic layer of scar tissue becomes stiff and inelastic, due to the disappearance of intercellular fluid (see Fig. 15). Since sound passing through the pedicle flap overlying a fenestra is influenced by the mobility of that tissue, which in turn is affected by the mobility of the continuous layer of connective tissue in the cavity, there is a drop in hearing. This drop, on the order of 5 to 10 db, is noticeable clinically and audiometrically almost immediately after a cavity has become dry. It is interesting to observe that if the ear becomes reinfected, with consequent return of intercellular fluid to the connective tissue, the hearing will resume its previous level. There are some fenestration patients, with poor healing in the cavity, who experience a drop in hearing even a year or two after the cavity has become dry. This is not always due to bony closure.

There is a final phase of shrinkage in the scar tissue which characteristically takes place one or two years after healing has occurred. This is secondary contracture, which results in further stiffness and diminution of elasticity. It is not necessarily the final fate of such connective tissue, since there is some evidence to indicate that scar tissue actually tends to regress,[4] and that in time elastic fibers grow into the region, restoring to it a certain degree of elasticity.

In the present uncertain state of our knowledge we need to be cautious concerning changes which take place in connective tissue. That changes do take place which have clinical significance and which are influenced by the type of healing, seems evident. These changes in connective tissue which can influence the elasticity of tissue overlying a surgically-made window to the inner ear cannot be ignored in the study of procedures to improve the physiology of hearing in deafened individuals.

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STAPHYLOCOCCUS BACTERIOPHAGE LYSATE AEROSOL THERAPY OF SINUSITIS.

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A fresh approach to the treatment of paranasal sinusitis is presented as a timely adjunct to the problem of infection caused by the antibiotic-resistant Staphylococcus (Micrococcus pyogenes var. aureus). A specific polyvalent bacteriophage lysate is administered by nasal aerosol, thus reaching the areas where this common pathogen is usually found, the anterior nares, as well as the respiratory tract. The paper draws upon the clinical experiences of the author and a number of associates, from the early use of this therapy in 1946 to the present. A fuller appreciation of the immunizing, hyposensitizing, and lytic possibilities of the lysate will help to clarify considerations justifying its use, and to reveal broader fields for clinical investigation.

BACKGROUND OF BACTERIOPHAGY.

After the discovery, by Twort and d'Herelle in 1915 and 1917, of the phenomenon of bacterial lysis by type-specific, parasitic, bacterial viruses, non-pathogenic to man, many different phages were isolated and put to therapeutic trial. Eaton and Bayne-Jones,[1] in a comprehensive review of the clinical data available up to 1934, expressed the opinion that the results were conflicting and difficult to assess. Krueger and Scribner[2] carried forward this cumulative survey to 1941, and their conclusions were equally critical; however, both papers called attention to the continuing favorable experiences with Staphylococcus bacteriophage, and thought it worthy of further study.

At about the same period, the therapeutic possibilities of this specific phage were strongly supported by MacNeal,[3]

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whose knowledge of, and confidence in the product, is reflected by his statement, "By the skillful use of bacteriophage, low-grade infections often are rendered trivial, acute infections may be aborted, deep-seated lesions may heal without drainage, and desperate conditions may be caused to heal in a surprising manner". He generally used and recommended intravenous administration. Other methods in vogue included the usual subcutaneous or intramuscular injections, wet dressings or sprays for superficial lesions, tamponades, inunctions, instillations or irrigations in body cavities and openings, and oral dosage for treatment of the gastrointestinal tract.

Herein is reported a technique for the aerosol administration of staphylococcus bacteriophage lysates, devised by the late Robert E. Lincoln, M.D., in 1946, for the treatment of infections involving the sinorespiratory tract. Admittedly, his presentation of the subject to the medical profession was incorrect; nevertheless, this paper is an attempt to overcome prejudice and to suggest a valuable contribution to medicine.

COMPOSITION AND PREPARATION.

Two staphylococcus bacteriophage lysates are prepared by the Lincoln Foundation Laboratory in Swarthmore, Pa. Primarily, the phage was the same in both; identified as Gratia B-985—from a stock collection maintained at the Boston University School of Medicine—and was selected because of its high polyvalency. As host cells for preparing the cultures, two strains of toxigenic staphylococci are used.

The A-1 lysate (Alpha) is prepared from a parent culture of S. aureus (Lincoln strain No. 1), originally obtained from the nasal passages of a patient with acute sinusitis and infectious diarrhea. The B-7 lysate (Beta) is made from a parent culture of S. aureus (Lincoln strain No. 7), first taken from a case of sinusitis with secondary infectious hepatitis. Both strains possess all the recognized characteristics of virulent toxigenic micrococci; they are coagulase-positive, produce exotoxins, alpha hemolysins, polysaccharides and penicillinase. The organisms are grown in beef-heart infusion broth and lysed by adding staphylococcus bacteriophage. When lysis is complete, the resulting solution is sterilized by filtration. To

insure viability of the phages, a preservative is not added. They retain full potency for at least three months, and keep well under ordinary refrigeration.

The final product has an extremely high lytic activity (phage content of 10^{-8} to 10^{-10}), and must pass all tests for sterility from bacteria, safety and absence of toxicity, in conformity with governmental requirements. Laboratory procedures are carried out under expert supervision by competent personnel, experienced in the preparation and quality control of biologics.

ADMINISTRATION AND DOSAGE.

For the treatment of sinusitis, staphylococcus bacteriophage lysate is administered as an aerosol by nasal inhalation. The mist is formed by releasing compressed air or oxygen into a Vaponefrin nebulizer, and is delivered into the nares through a Y tube with glass nasal tips. It is usual to start treatment with the inhalation of .25 cc. of the Alpha lysate. Subsequent doses are gradually increased at one to three-day intervals, until the full maintenance of 1 cc. is reached. If progress is not continuous, the Beta lysate may be added for fuller effect.

It is emphasized that determination of dosage and the interval is highly individualized, depending upon the post-treatment reactions. Patients are told they may have transient episodes of malaise, especially during the early stages of the therapy, that occur as a rule, about four to six hours after an inhalation. They vary from fatigue with mild aches and pains, to a more severe type with chills followed by slight fever of short duration, grippe-like symptoms and more marked general discomfort, easily relieved by medication. There may be temporary reactivations of any previous illness, due to sensitization phenomena. Reactions, which last from a few minutes to a few hours, tend to disappear as treatment progresses and are succeeded by a feeling of well-being. The more uncomfortable ones indicate a reduction in the amount of phage given, temporarily, or a lengthening of the treatment interval. Post-treatment effects are due, in part, to local bacteriolysis, with a release of toxins which stimulate the production of specific antibodies, and to a bacterial desensitization.

The aerosol therapy should be continued until reactions cease, or till relief from all symptoms, objective and subjective, is realized. When definite alleviation has been established, a monthly maintenance or booster dose tends to forestall and prevent relapses and to lessen the number and the severity of head colds.

ADJUNCTIVE MEASURES.

During the course of treatment, daily nasal irrigations with warm dextrose solution are advisable to clear the passages of mucus and crusts, and to prepare the mucosa for the absorption of the lysates. Specific written instructions are issued to the patient for this home procedure. If diarrheal symptoms accompany the sinusitis, the Alpha lysate is used orally in 1 to 2 cc. dosage in 30 to 60 cc. of water. Taken with one-fourth to one-half grain (.015 to .030 gm.) codeine sulfate, the phage has proven to be an exceptional aid in combatting the infectious diarrheas, so often present in such conditions, and in staphylococcal enterocolitis.

The usual supportive measures, as a diet rich in protein, adequate rest, prevention of calcium and vitamin deficiencies, and relief of nervous tension, are requisite. Other hyposensitizations, the use of antihistamines and antibiotics orally or parenterally, in no way inhibit the action of the bacteriophages, which should be looked upon as an auxiliary to other necessary therapy.

CLINICAL OBSERVATIONS.

The results of staphylococcus bacteriophage lysate aerosol therapy in 60 cases of chronic sinusitis are summarized. They constitute a random sampling of patients who had proven stubborn to conventional treatment, and include 26 males and 34 females. The youngest was six years of age, the oldest, 70, and the average age for the group was 40. The number of aerosols ranged from five to 90 per patient, with an average of 18 treatments. In 27 cases (45 per cent) the results were rated as excellent, in 20 (33 per cent) good, in 10 (17 per cent) fair, and in three (5 per cent) poor. For the combined groups of good to excellent, the percentage is 78 per cent.

In agreement with clinical observations made at the Lincoln Foundation clinic, physicians using the phages report numerous cases that had been resistant to all other treatment made satisfactory improvement within two to six weeks, or after 10 to 20 inhalations. Intrafamilial cross infection must be considered in the recurrent case under treatment, and contacts should be advised to have the therapy, even though they may not be ill due to a high level of antibody production.

CASE REPORTS.

The following case is of special interest because it presents a severe staphylococcal infection of the nasopharynx, with membrane formation, super-imposed on and masking a chronic sinusitis.

Case 1: E. D., a six and a half-year-old girl was seen by the author on an emergency call the early morning of Aug. 6, 1953, because of nausea, vomiting and a severe croupy cough of three days' duration. At age six, the onset of sinusitis had been noted, with frequent colds, constant post-nasal drainage, poor appetite and lack of vigor. Four attacks of tonsillitis had occurred since March, 1953, coincident with acute exacerbations of the sinusitis. Swollen cervical glands were present with each illness and did not subside entirely afterward. July 21, she became sick with a sore throat, stuffy nose, a temperature of 101° F. and severe lassitude. Bilateral cervical adenitis developed rapidly. The family physician was called and gave 300,000 units of procaine penicillin, intramuscularly, and 400,000 units by mouth, on two successive days. He then went on a scheduled vacation.

The child was frail, toxic, and orthopneic with stertorous breathing. The lips and fingers were moderately cyanosed, this condition having become more noticeable to the mother during the night. Temperature was 101° F., pulse 120 and weak. A thick grayish-white membrane, which bled on removal, covered the fauces, tonsils, pharynx, and extended upward into the posterior nares. The nasal passages were blocked by this same membrane. Because of the emergency, 40,000 units of diphtheria antitoxin were given, though immunizations had been received at the age of one year, with a booster at age three. Procaine penicillin, 1,000,000 units, was administered intramuscularly once only, because she developed a reaction to it. Syrup of ipecac induced vomiting and expectoration of considerable phlegm, with great relief from the stridulous breathing. Steam inhalations, containing Alevaire, were kept going constantly for the first 24 hours. Diphenhydramine (Benadryl) 25 mg. was given orally for its sedative and antihistaminic effect. Alevaire was also used by mouth as an aerosol, to loosen mucus.

Two cultures of the nose and throat showed a pure growth of S. aureus. After douching the passages with warm dextrose solution, 1 cc. of the Alpha bacteriophage was administered by nasal aerosol and inhaled orally, 1 cc. of the Alpha lysate in 30 cc. of water was taken by mouth, because of diarrhea, present two days. The phage lysate was given once a day nasally and orally, for 11 days, then on alternate days for four doses. At this time, the family physician returned, and the treatments were discontinued.

Within 24 hours after starting the phage therapy, the child was resting comfortably, with no orthopnea or cyanosis. Fluids were taken easily, and in 36 hours soft solids were added. The diarrhea subsided in 48 hours and the stools became normal. The tenacious membrane sloughed off with remarkable ease and in three days had entirely disappeared. The cervical adenitis seemed to melt quickly, noticeably decreasing within 24 hours, and in one week was gone. Interest in surroundings and play returned within 48 hours, with a rapid lessening of toxicity. Post-nasal discharge and other symptoms of sinusitis cleared within one week; the only residual sign was a mild anemia, and the girl was apparently well. Two months later it was learned that there were no after-effects, further treatment had not been required, no sinusitis or adenitis was present and she had gained six pounds in weight.

The average case of sinusitis with bacterial allergy is illustrated by the following report from A. G. Baker, M.D., Ridley Park, Pa., and is used here with his permission.

Case 2: J. H. W., a business executive, age 45, came under Dr. Baker's care Sept. 30, 1952, complaining of copious post-nasal drip, severe headaches on occasion, morning cough and increasing difficulty with hearing. Onset occurred early in 1950, with an acute attack of sinusitis. Previous treatments by otolaryngologists included surgery for correction of a deviated septum and to provide a maxillary window. These, and the usual ear, nose, and throat regimen gave only temporary relief. The diagnosis of sinusitis was confirmed, both frontal and maxillary tenderness being present. Cultures from the nose yielded a growth of S. aureus, with some hemolytic streptococci. The hemoglobin was 84 per cent, sedimentation rate 8 mm. in one hour, RBC and WBC totals normal. Neutrophiles were low (34 per cent) while lymphocytes were increased (62 per cent). There was no increase in eosinophiles, though skin tests showed moderate reactions to house dust, orris root and feathers.

Staphylococcus bacteriophage lysate aerosol therapy was started on Oct. 6, 1952. Inhalations were given daily to October 21, and then at two to five-day intervals until December 6—a total of 23 treatments in eight weeks. Concurrently, a course of six hyposensitizing injections (house dust extract and a serobacterin) was given at intervals of a week or more. The patient experienced reactions after a few of the early aerosol treatments; some were mild grippe-like symptoms; others were more severe but of short duration, with chills, slight fever and aching joints. Within five days there was general improvement, with less post-nasal drainage, the cough had stopped entirely and sinus tenderness had abated. Further gradual relief followed, not only in the sinusitis, but his hearing also was definitely benefited in ten days, and after four weeks was reported "perfect." He was asymptomatic by December and bacteriophage treatments were discontinued after Dec. 6, 1952. A follow-up inquiry in late 1954 noted that he was feeling fine and was free of sinus trouble.

DISCUSSION.

Latent Infection.

While the literature on sinusitis is voluminous and often confusing, nevertheless, there is general agreement on many basic points.[4] It is acknowledged that normally the nasal mu-

cosa harbors a mixed flora of pathogenic and non-pathogenic organisms. In health these are apparently harmless, being held in check by the combined effects of ciliary action, the slightly acid pH of nasal secretions, the lysozyme present in mucus, and a balanced antigen/antibody ratio. Vital resistance may be lowered by physiologic disturbances or stress: exhaustion from previous disease, trauma, surgery, shock and old age; mental or physical fatigue and menstruation; malnutrition, vitamin deficiencies and the extended use of the broad-spectrum antibiotics; prolonged nervous tension, and especially by exposure to extremes of wet and cold weather, high humidity having the greatest influence.

The foregoing provoking factors favor the growth of these dormant microorganisms; virulence increases, invasion of tissues and infection of sinuses take place. Interference with ventilation and drainage causes a toxic absorption, which is reflected in pain and malaise, with lassitude, weakness and general ill feeling.[5]

Many references are in accord that the staphylococcus is the pathogen most frequently isolated from the nose, often dominant and probably the most virulent.[6-9] Welch[10] states, "The organism is ubiquitous and probably is the cause of more infections in man (not excluding the common cold) than any other known microorganism".

Bacterial Allergy.

Similarly, there is a general agreement that, "70 to 80 per cent of all cases of chronic sinusitis have allergy as their basic pathology. There is no doubt but that bacterial infection of the respiratory tract may cause hyperplastic sinusitis and asthma".[11] Allergy, particularly bacterial allergy, plays an important role in nasal and sinus disease, because the resulting edema and hyperplasia of the mucosal layers close the ostia, block drainage, impair ventilation and ciliary action, favor infection and build up internal pressure, which in turn increases toxic absorption. In the majority of cases of sinusitis, the process is one of allergy combined with infection.[4, 12-16]

Swineford and Holman,[17] reporting on a large series of cutaneous reactions to the polysaccharide and nucleoprotein fractions of 14 different bacteria, found that skin tests for bacterial allergy gave both immediate and delayed reaction types. The larger number, and the higher percentage of the immediate reactions, were elicited by the polysaccharides of S. aureus. Delayed or tuberculin-type reactions also were frequently induced by the nucleoproteins of the same organism. In later studies on bacterial allergy, Swineford,[18] using pneumococcal polysaccharide experimentally on passively sensitized guinea pigs, demonstrated that, "Desensitization may be readily produced by specific hapten aerosol". This study has a direct and important bearing on the sinusitis problem and favors the assumption that staphylococcal polysaccharides and nucleoproteins in the bacteriophage lysates may act as specific antigens in the bacterial allergy associated with this disease. The supposition requires further laboratory and clinical research for its corroboration.

Baker,[19] in a series of 60 cases of chronic bronchial asthma and sinusitis treated by aerosol inhalation of these phage lysates, found the therapy afforded sustained symptomatic relief in every instance, when used as an adjunct to other desensitization measures. No evidence of toxicity, local irritation, or anaphylactic-type reaction was apparent during the course of treatment. In a series of six asthmatic patients, he gave aerosols with the culture medium alone, without relief.

Staphylococcus Toxin and Vaccine Action.

Lucic[20] and Burky[21] were able to show that substances with mild antigenic properties might become activated if combined with staphylococcus toxin. Also, Blair[22] states, "In common with some other pathogenic bacteria, staphylococci produce a spreading factor (Duran-Reynals, 1942) which, by increasing the permeability of connective tissue, aids in the initial formation of the local lesion. The spreading factor is related to the mucolytic enzymes, or hyaluronidase, and is similar to a spreading factor found in testicle and other body tissues. . . . Experimental infections with other bacteria or with viruses are enhanced by staphylococcic spreading factor."

According to Larkum,[23, 24] a superior vaccine is prepared by lysing an organism. Lytic filtrates possess an antigenic capacity, in that they induce specific neutralizing antibodies, which have many of the attributes of an antitoxin. It is the bacteriophage itself which has this property. Phage combines with strain-susceptible bacteria, and initiates a change which progressively renders them more amenable to phagocytic ingestion. The more potent the phage, the greater this action becomes.

Formerly, bacteriophages were utilized mainly by injection, and the system, perforce, formed antiphage (antilysin) which gradually prevented phagic lysis to a degree. When used as an aerosol, intranasally, the development of antiphage is slowed as the mucosal lining of the sinorespiratory tract has a chance to select or reject fractions of the lysate.

Mucous Membrane Absorption.

As a means of drug administration, the nasal mucous membranes permit the passage of many antigens, serums, toxins, toxoids, pollen extracts, vitamin B_{12} and others. Chait and Walzer[25] have shown that this absorption is fast. Tonndorf et al.,[26] in testing various drugs to combat motion sickness, found that absorption in this area was more rapid than after oral administration, that it approached more nearly the speed of subcutaneous injection, and that a smaller dose was required than by mouth. Ease of administration and rapidity of absorption have been repeatedly emphasized. Clinical observations indicate that this is equally true of the phage aerosols used in this study.

COMMENT.

Bacteriophages make a relative immunity, in which the recovery is not complete. This active resistance to infection, or non-sterile immunity, is characterized by the fact that the antibodies produced are sufficient to suppress the majority of susceptible pathogens, but leave a few resistant organisms, which are subsequently able to repeat the infection, under conditions of physiologic stress. This is the reason for maintenance or booster treatments. Regardless of the varying phage sensi-

tivity of staphylococci, the active immunization value of the lysates is based upon their close antigenic relationship.

All available staphylococcus phages (used for classification purposes) have been tested for lytic ability, and none compare with the high polyvalency exhibited by these preparations. Phage resistance has not occurred among many strains of micrococci tested in the laboratory. The effectiveness of these bacteriophages in therapy is in no way limited by the antibiotic resistance of the prevailing strains of S. aureus.

The basic premise for the use of bacteriophages in general was that bacterial viruses on parenteral injection, would lyse their specific host cells anywhere in the body. It is now realized this occurs only on actual contact, and the good results previously obtained were due to a specific immunizing action, an increase in susceptibility to phagocytosis and to a hyposensitizing effect.

The application of the lysates, by nasal aerosol, was originally chosen as an effective method of treating sinusitis. Through clinical observation of a large number of patients thus afflicted, it was noted that certain collateral symptoms, or concomitant disease entities, were also improved or eliminated as the foci of infection in the paranasal sinuses were cleared. These observations will be the topic of a future paper.

SUMMARY AND CONCLUSIONS.

While the use of strain-specific bacteriophage lysates or filtrates is not new, the emphasis in this report is on their administration by nasal aerosol inhalation for the treatment of paranasal sinusitis. The earlier literature refers to the use of phages in the form of nose drops, packs and irrigations as a means of local application to the nasal passages and sinuses. Reviews are conflicting as to their value, but do call attention to the continuing favorable experiences with staphylococcal types.

Clinical observations of patients having chronic sinusitis, treated with staphylococcus bacteriophage lysates prepared by a special method, show gratifying results in 78 per cent of cases. These were stubborn conditions that had not been re-

lieved by a conventional regimen. Oral use is an exceptional aid in combatting infectious diarrhea, commonly found with sinusitis, and in staphylococcal enterocolitis.

The preparation, administration and dosage are outlined. The aerosol is given by standard intranasal technique under a pressure of five to six liters of air or oxygen per minute, thereby reaching all the available surfaces of the nasal mucosa, sinuses, bronchi and the lungs on inhalation. In this manner, an effective local concentration of the bacterial viruses is made to the areas where the principal pathogen, staphylococcus aureus (micrococcus pyogenes var. aureus), is most numerous; the anterior nares being the chief reservoir of these potentially virulent microorganisms in health and in disease. Latent infection in the paranasal sinuses, activated by various physiologic disturbances or stress factors, may be the site of parenteral introduction of bacterial protein with a consequent sensitization of the body tissues. Staphylococcal spreading factor may enhance infection with other bacteria or viruses.

The rationale for the use of staphylococcus bacteriophage lysate by nasal aerosol and oral dosage takes into consideration certain advantages and potentialities that reveal broader fields for clinical investigation:

The bacteriophage used in preparing the biologic is a well established and actively polyvalent strain that has a lytic effect over a wide spectrum of pathogenic and non-pathogenic staphylococcal groups.

The phage is antigenic; mucous membrane absorption produces a more effective and rapid active immunization than the injection of an orthodox vaccine. The selective powers of the nasal mucosa minimize the possible development of antiphage (antilysin).

The lysate is anti-allergic; certain constituents, such as polysaccharides and nucleoproteins, act as haptens or partial antigens, and bring about a gradual hyposensitization to micrococcal bacterial allergy, which is present in 70 to 80 per cent of sinusitis cases.

The immunizing and hyposensitizing results are exerted against all strains of micrococci because of their close anti-

genic relationship, regardless of their varying sensitivity to phagic lysis. The development of resistance to the lysates has not occurred in laboratory tests.

Staphylococcus bacteriophage lysates administered by nasal aerosol and oral technique are stressed as a valuable adjunct to the treatment of the antibiotic-resistant micrococci.

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ANNUAL ASSEMBLY IN OTOLARYNGOLOGY.

The Department of Otolaryngology, University of Illinois College of Medicine, announces its Annual Assembly in Otolaryngology from October 1 through 7, 1956. The Assembly will consist of an intensive series of lectures and panels concerning advancements in otolaryngology, and evening sessions devoted to surgical anatomy of the head and neck, and histopathology of the ear, nose and throat.

Interested physicians should write direct to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Ill.

ABLATION THERAPY FOR THE RELIEF OF MENIERE'S DISEASE.*†

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Detroit, Mich.

A sudden attack of severe vertigo, accompanied by vomiting, can be a terrifying experience. When the episodes in Ménière's disease recur frequently the patients become very apprehensive for fear of having an attack while at work or on the street. At this stage they are incapacitated, and quite willing to make some sacrifice to acquire relief of symptoms.

The diagnostic criteria for Ménière's disease include tests for auditory and vestibular function. It is these tests, in fact, which make it possible to differentiate Ménière's disease from other vertiginous disorders. The criteria may be listed as follows:

1. Attacks of vertigo and vomiting.

2. Perceptive type hearing loss, manifested by threshold loss for bone and air conduction.

3. Loudness recruitment in the involved ear.

4. Diminution of caloric response in the involved ear.

These criteria must be met before ablation therapy can be advised. The classical symptoms of Ménière's disease are well-known to all of us, and need no further description at this time.

It is not my purpose to discuss the medical management of this disease. We all recognize that medical management is fairly successful in many patients, and it should be used first,

* Read at the Sixtieth Annual Meeting of the American Laryngological, Rhinological and Otological Society, Inc., Montreal, Can., May 17, 1956.

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† This is a summary of the studies completed to date and the conclusions reached. A complete report is in preparation.

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resorting to ablation methods only if vertiginous attacks continue to incapacitate the patient.

The mechanical receptors for both the vestibular and auditory systems operate on hydrodynamic principles and have attained, therefore, an intimate anatomical relationship in the labyrinth to the temporal bone. For this reason surgical attempts to ablate the vestibular system and leave the auditory structures intact have not been uniformly successful; nonetheless, there are several procedures which have as their object the selective destruction of vestibular function and preservation of hearing. Two methods should be mentioned. *1.* There are reports from Italy of good selective destruction of the vestibular system with a technique utilizing high intensity ultrasonics.[1] To my knowledge it has not been used in this country. *2.* By sectioning the vestibular nerve it is possible to preserve pure tone thresholds at the preoperative levels in some patients. To my knowledge, however, there has been no evaluation of speech discrimination following vestibular nerve section. Testing of speech intelligibility is particularly important where there is possibility of injury to the cochlear nerve. It is now fairly well established that a decrease in nerve fibre population to the cochlea results in a loss of auditory discrimination out of proportion to the loss for pure tone thresholds. Following vestibular nerve section I would like to know, not only the level of pure tone thresholds, but also the speech discrimination scores. Has practical hearing been preserved?

Before labyrinth ablation for unilateral Ménière's disease is undertaken the following criteria should be met:

1. The diagnosis should be established conclusively through history and characteristic auditory and vestibular findings.

2. The symptoms must be at least moderately incapacitating.

3. The auditory function of the opposite ear must be good without evidence of progressive disease.

TRANS-TYMPANIC LABYRINTHOTOMY.

Trans-tympanic labyrinthotomy is the simplest effective surgical method of destroying inner ear function. The tech-

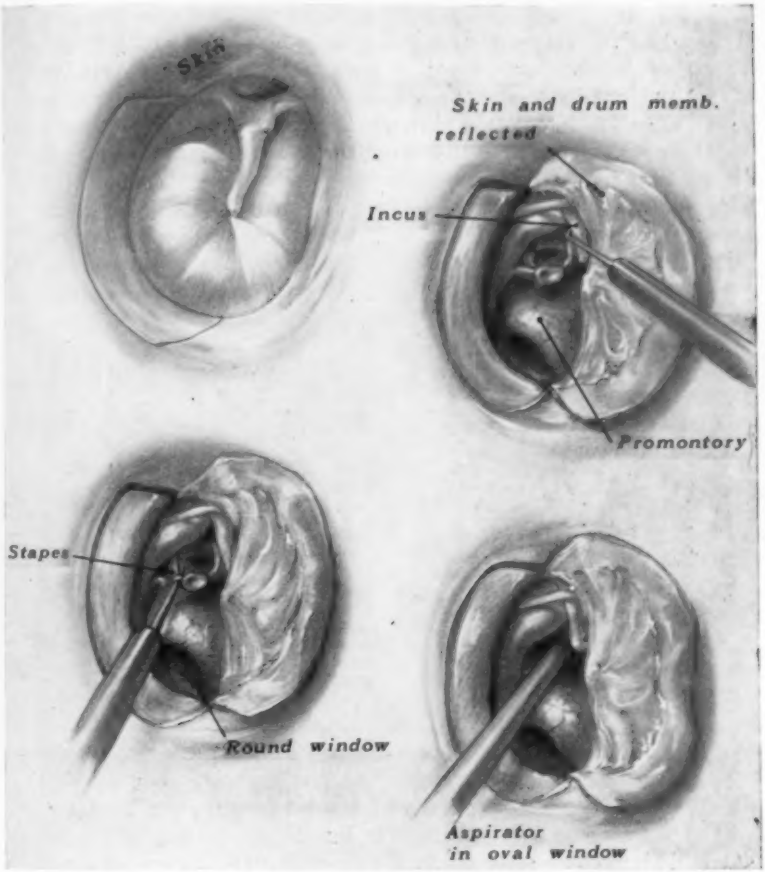

Fig. 1. Surgical procedure for trans-tympanic labyrinthotomy. See text for explanation.

nique varies slightly from the original trans-tympanic technique described by Lempert.[2]

An endaural incision is made as for the stapes mobilization, and the middle ear is exposed (see Fig. 1). The incudo-stapedial joint is disarticulated by displacing the long process for-

ward. The stapes tendon is cut with an endaural scissors. The head of the stapes is engaged with a needle and with gentle manipulation it is loosened. A hook is then introduced into the intracrural space and the stapes removed. A small barbed instrument is introduced through the round and oval windows and manipulated so as to disrupt the membranous labyrinth. A suction tube is introduced through the oval window and the contents of the vestibule aspirated. Small pieces of gel-foam are placed in the vestibule to stimulate connective tissue proliferation and acquire thereby a firm barrier between the middle ear and subarachnoid space. The operating time is about 20 minutes.

TABLE I. TRANS-TYMPANIC LABYRINTHOTOMY.

Case	Method	Caloric	Hearing	Recurrence	Follow Up
1	Opened	Lost	Lost	No	19 mo.
2	Windows	Decr.	Lost	Yes (7 mo.)	19 mo.
3	Only	Lost	Lost	No	18 mo.
4		Decr.	Lost	Yes (12 mo.)	18 mo.
5	Probed	Lost	Lost	No	14 mo.
6	and	Lost	Lost	No	14 mo.
7	Aspirated	Lost	Lost	No	11 mo.
8	Inner	Lost	Lost	No	10 mo.
9	Ear	Lost	Lost	No	9 mo.
10		Lost	Lost	No	8 mo.
11		Lost	Lost	No	3 mo.
12		Lost	Lost	No	3 mo.
13		Lost	Lost	No	2 mo.

During the past 19 months this operation has been performed on 13 patients with incapacitating unilateral Ménière's disease. The operative procedure in the first four patients consisted only of removing the stapes and rupturing the round window membrane without probing and aspiration (see Table I). In two of these a mild caloric reaction to ice water remained in the operated ear after surgery. Both patients had recurrence of dizzy spells, although the attacks were less frequent and less severe than before surgery. A second operation including probing and aspiration of the inner ear resulted in total loss of caloric reaction and relief of symptoms. There was total loss of caloric reaction to ice water and relief of dizzy spells in all patients in whom the contents of the vestibule were probed and aspirated. The average age of these 13

patients was 53 years, average hospital stay seven days, average duration of symptoms prior to operation four and one-half years, and the average time lost from work after operation 23 days.

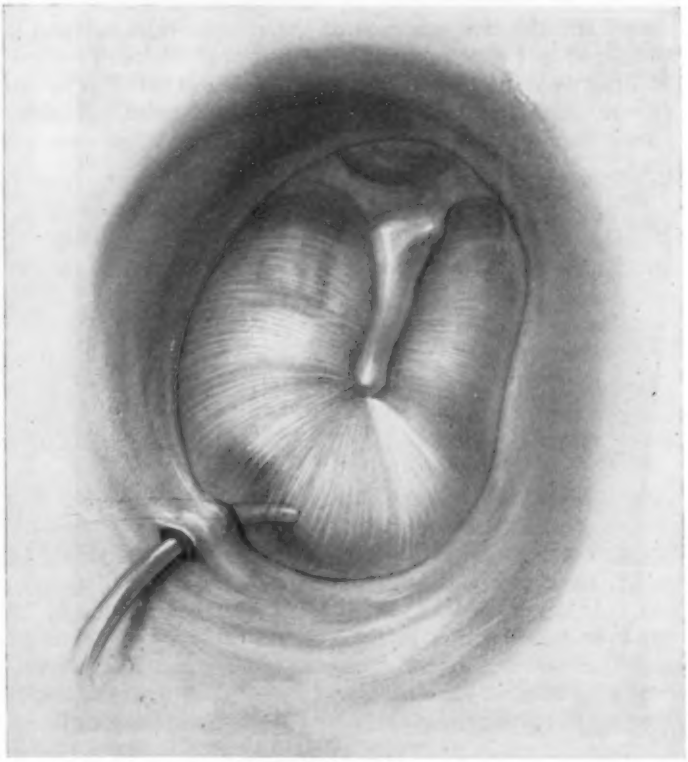

Fig. 2. Intra-tympanic steptomycin therapy is given through tubing which is introduced into the middle ear through a knife wound made through the annulus tympanicus.

INTRA-TYMPANIC STREPTOMYCIN.

An equally effective method of accomplishing unilateral labyrinthine ablation is intra-tympanic streptomycin therapy. The drug is injected through small plastic tubing which has

been introduced into the middle ear through a small knife wound in the annulus tympanicus (see Fig. 2). This tubing has an outside diameter of .61 mm. and inside diameter of .28 mm.* The tubing has been left in place as long as seven days without discomfort, and leaves not even a temporary perforation after removal. By varying the frequency of injection and the concentration of the streptomycin solution it was hoped that a method might be developed whereby vestibular function could be destroyed and hearing saved. The results showed that successful treatment depends upon abolishing caloric reaction to ice water (see Table II). When this was

TABLE II. INTRA-TYMPANIC STREPTOMYCIN.

Case	Gm./cc.	Days Therapy	Caloric	Hearing	Recurrence	Follow Up
1	.5	1	Same	Same	Yes	20 mo.
2	.5	2	Same	Same	Yes	20 mo.
3	.5	2	Same	Same	Yes	10 mo.
4	.5	3	Lost	Lost	No	7 mo.
5	.5	4	Lost	Lost	No	5 mo.
6	.125	7	Lost	Lost	No	4 mo.
7	.125	6	Lost	Lost	No	3 mo.
8	.125	7	Lost	Lost	No	3 mo.

accomplished hearing was also lost. The first three patients received inadequate therapy; the caloric responses were unchanged or slightly decreased, and recurrences followed. Of the five cases receiving adequate therapy the longest follow-up was only seven months, but in view of the total loss of ice water caloric reaction in the treated ears, a recurrence of symptoms seems unlikely. The results suggest that the treatment may be most effectively accomplished by injecting about .1 cc. of streptomycin every four hours in a concentration of .5 grams per cc. in physiological saline, with injections being given for one day beyond the stage when vestibular symptoms are fully developed. That would be about four to five days. The vestibular reactions and after-effects of treatment are identical to those following labyrinthotomy. The procedure has one distinct advantage over labyrinthotomy in that a general anesthetic is not required.

* Polyethylene tubing, size PE-10, Clay-Adams Co., Inc., 14 E. 25th St., New York 10, N. Y.

In an experiment in which a number of cats were given intra-tympanic streptomycin it was found that there was a total loss of hair cells in both the vestibular labyrinth and cochlea (see Fig. 3).

PARENTERAL STREPTOMYCIN THERAPY.

The treatment of patients with bilateral Ménière's disease is a different problem, for here it is imperative that all existing auditory function be preserved. This is best accomplished

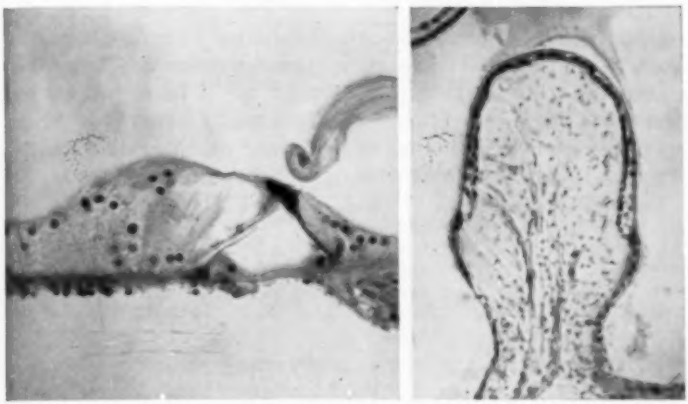

Fig. 3. Organ of Corti and crista ampullaris of a cat given one injection into the auditory bulla of one-half cc. of physiological saline containing 0.25 gram of streptomycin sulfate. There was a total loss of hair cells in the inner ear.

by parenteral streptomycin therapy, by which it is possible to selectively destroy the vestibular function in both ears and save hearing. Previous reports of moderate success from the use of streptomycin for Ménière's disease have been made by Fowler,[3] Hamburger et al.,[4] Ruedi[5] and Hanson.[6] My experience with the drug has more or less paralleled theirs.

Several of the first patients received three gm. per day for part of the treatment period, but in this dosage the onset of toxicity was too precipitous to allow for satisfactory control of the end result. The ideal quantity was considered to be 2

gms. per day, given intramuscularly in two equally divided doses, for this resulted in a more gradual development of toxic effect with the desired end-point being reached in two to four weeks. The treatment was given for seven to ten days on an out-patient status, after which the patients were admitted to the hospital where more careful observation was possible.

The importance of frequent auditory and quantitative caloric testing cannot be over-emphasized. I found no advantage in routinely performing both hot and cold caloric tests. The minimal caloric tests were used, which were performed by injecting 5 cc. of water at 80° F. against the postero-superior quadrant of the eardrum at a rate of $\frac{1}{2}$ cc. per second, and observing the nystagmus through illuminated Frenzel glasses in a darkened room. The reaction time was recorded from the end of injection to the end of nystagmus. If there was no reaction to 80° F. water, then 5 cc. of ice water were used. When spontaneous nystagmus existed, the ear on the side opposite the direction of the quick component was tested with water at a temperature of 118°.

TABLE III. PARENTERAL STREPTOMYCIN.

Case	Therapy Days	Caloric Right	Caloric Left		Recurrence	Follow Up
UNILATERAL						
1	21	Decr.	Lost	†	No	57 mo.
2[1]	7	Lost	Decr.	††	No	45 mo.
3	36	Decr.*	Lost	††††	No	37 mo.
4	26	Lost*	Decr.	††	No	29 mo.
5	14	Decr.	Lost*	†††	No	28 mo.
BILATERAL						
6	24	Decr.*	Decr.*	†††	No	34 mo.
7	12	Decr.*	Decr.*	††††	No	14 mo.
8	15	Lost*	Lost*	††††	No	12 mo.

1 Given 3 grams per day. Decr. Decreased. * Diseased ears.

For the five patients with unilateral Ménière's disease the streptomycin was discontinued on the first day the ice water caloric failed to give a response in the diseased ear. Four of these patients experienced a total loss of ice water caloric reaction in the diseased ear with some preservation in the normal ear (see Table III). The three patients with bilateral Ménière's disease were treated with the objective of preserv-

ing some function in one or both ears. This was accomplished in two patients. A remarkable result was the sustained improvement in auditory thresholds in five of the eight cases. This improvement was not important for the unilateral cases,

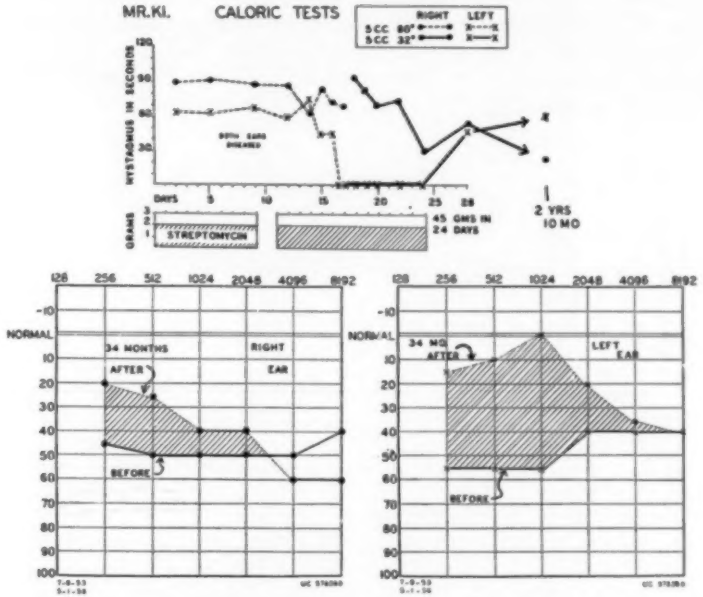

Fig. 4. Above: Results of minimal caloric tests of patient with bilateral Meniere's disease. The tests were performed by injecting 5 cc. of water against the eardrum and measuring the time lapse from end of injection to end of nystagmus. Note that 80° F. water was used for 16 days, after which it was necessary to use ice water to get a response. The intramuscular streptomycin injections were discontinued on the 24th day, when there was no reaction to ice water in the left ear and a mild response in the right ear. Two years and ten months later a slight caloric response to ice water remained in both ears. He has had no further dizzy spells.

Below: Audiograms showing remarkable recovery of thresholds. The results were confirmed by multiple tests on different days, both before and after treatment.

but for one patient with bilateral Ménière's disease the remarkable improvement in auditory thresholds was most gratifying (see Fig. 4). The results indicated that the patients in whom some vestibular function was preserved experienced less ataxia and yet had an equally successful relief from ver-

tiginous attacks. The greatest problem encountered in parenteral streptomycin treatment was prolonged ataxia. The patients with the greatest loss of caloric response had the most severe ataxia. All eight patients treated by this method were discharged from the hospital within one week following treatment. Ataxia was moderately severe for two to three months in all cases. Three were unable to perform normally in their occupations for nine to 12 months. Most were able to drive their autos in two to three months, although one patient required ten months. They all returned to work within periods

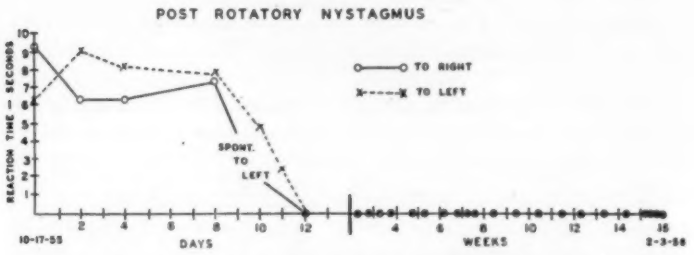

Fig. 5. Post-rotatory nystagmus plotted against time for a cat receiving 200 mgm. per kg. of streptomycin injected intramuscularly in two equally divided doses. Post-rotatory nystagmus was measured from the end of rotation (10 turns in 10 seconds) to the end of nystagmus. Streptomycin was discontinued on the tenth day. Post-rotatory nystagmus was absent on the twelfth day, and no reaction could be elicited during the following two months. On the tenth and eleventh days there was spontaneous nystagmus to the left, so that the turning test to the left was omitted. Auditory thresholds for the experimental ear (right), as determined by the behavioral method,[7] remained normal throughout. The function of the left ear was destroyed by a surgical procedure four months before the beginning of the experiment.

of time varying from two to nine months. All patients have been completely relieved of vertiginous attacks, the longest follow-up being four years, nine months. Three of eight patients have had attacks of tinnitus and fullness in the ears simulating the auditory symptoms existing prior to treatment. The undesirable symptoms coincident with total loss of vestibular function subsided gradually, so that after one to two years the patients were essentially asymptomatic.

Parenteral streptomycin therapy is not recommended for unilateral Ménière's disease because an equally effective result

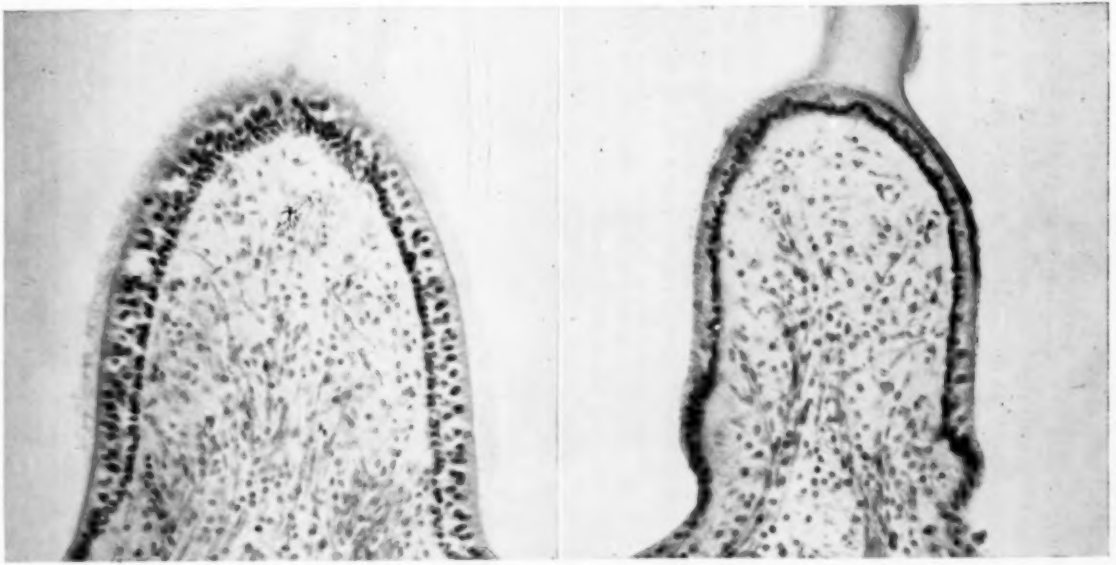

Fig. 6. Left: Normal crista ampullaris from an untreated control cat.
Right: Loss of hair cells in crista ampullaris of cat receiving intramuscular streptomycin whose nystagmogram appears in Fig. 5. The utricular and saccular sensory epithelium were similarly degenerated. The organ of Corti was normal throughout.

can be accomplished by unilateral labyrinth ablation with less subsequent vestibular upset.

Preliminary studies of an experiment in which streptomycin was given parenterally to cats has revealed that vestibular function can be destroyed and hearing preserved with a good margin of safety. Pathological study has revealed destruction of the vestibular sensory epithelium and preservation of a normal organ of Corti* (see Figs. 5 and 6).

I gratefully acknowledge the generous help of Dr. Roderick C. Davison, of Winnipeg, and Mrs. Rosemary Doran, Dr. Joyce White and Dr. T. Manford McGee, of Detroit, with the animal experiments.

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* The results of the animal experiments on streptomycin ototoxicity are incomplete, and the findings presented here should not be interpreted as conclusive. The question of possible streptomycin damage to the brain is also under investigation.

PAPILLOMATA OF THE LARYNX.*

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Dayton, Ohio.

Perhaps no other laryngeal condition has given rise to greater diversity of conflicting observations and conclusions than has papilloma of the larynx. A study of the literature throws surprising light on current theories of etiology and methods of treatment.

HISTORICAL BACKGROUND.

Surprisingly enough, the condition was recognized long before the invention of the laryngoscope: sometime during the Seventeenth century Marcellus Donalus wrote of laryngeal growths describing them as "warts on the throat."[1]

When, early in the nineteenth century, the Imperial Government of France offered a prize for the best study of croup, one far-reaching result was the considerable impetus given to the investigation of laryngeal growths.[2] The first case of papilloma of the vocal cord reported in the United States was published by Cheesman of New York, in 1817;[3] the patient died without relief. Two decades later Trousseau and Belloc published their review of seven cases, the total reported up to that time.[4] In 1850, Ehrmann published a complete monograph on growths of the larynx,[5] but how many of these were papillomata we are unable to say.

A landmark was reached in 1866, when Elsberg published the first description of the microscopic appearance of laryngeal papilloma,[6] but use of the term "papilloma" may be sus-

1. Selwyn-Brown: The Physician Throughout the Ages, Vol. II, pp. 455-456. For full data see Bibliography appended.
2. Mackenzie: Essay on Growths in the Larynx, pp. 2-5.
3. Broyles: Trans. Am. Acad. Ophth., Jan.-Feb., pp. 247-253, 1948.
4. Selwyn-Brown, op. cit., p. 457.
5. Mackenzie: op. cit., p. 5.
6. Selwyn-Brown: op. cit., pp. 455-457.

* Submitted as Candidate's Thesis to American Laryngological, Rhinological and Otological Society, Inc., 1956.

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pect until at least 1871, when benign growths of the larynx were first differentiated and classified in Mackenzie's report of 100 collected cases.[7]

RISE OF CONFLICTING OPINIONS.

There must have been almost immediate and universal unanimity as to the symptoms, gross appearance, and histology of papilloma of the larynx, since there has been little variation in discussions of these matters since the time of the earliest published reports; but at that point agreement ceased. Statements as to etiology have ranged from a firm belief in either chronic irritation,[8] chronic inflammation,[9] nasal obstruction,[10] or a constitutional diasthesis,[11] to a candid admission that the cause is yet to be determined; nor is the latter belief the most ancient.[12] Between these extremes, enough case reports have linked a specific trauma[13] or a particular infection[14] with the subsequent development of papilloma to further cloud the picture of etiology.

In like manner, authorities have differed greatly on the sex preference and the age incidence of this disease. Frequently it has been stated that these growths are more common in males;[15] but at least one observer found just the opposite to be true in his series of cases,[16] while reports from other sources indicate little, if any, sex preference.[17] Many authorities consider the disease primarily one of infancy and early child-

7. Early writers, such as Bosworth and Shurly, agree that Mackenzie was first to perform this service.

8. Ehrmann and Horace Greene: cited by Mackenzie, op. cit., pp. 8-9.

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11. Brose: J.A.M.A. (reprint), 44:874, 1905.

12. See Babcock: Surg. Clin. North America, 14:301-306, 1934; New and Erich, loc. cit., 1934; Ferguson and Scott, New Eng. Jour. Med. 230:477-482, April 20, 1944; Green, Med. Jour. Australia, 1:627-628, May 2, 1953; Rubin, Canad. Med. Assoc. Jour., 71:572-575, Dec., 1954.

13. See El Mofti: Laryngeal Polpoid Growths Following Endotracheal Anesthesia, Jour. Laryngol. and Otol., 63:759-761, Dec., 1948. He reports eight cases from the literature and adds one.

14. Ballinger, in Diseases of the Nose, Throat, and Ear, p. 542, noted measles to be "apparently a prolific exciting cause" of laryngeal papilloma.

15. Opinions expressed by Ballinger, Babcock, and Rubin, in the respective works or places previously cited.

16. Ferguson: loc. cit.

17. New and Erich: loc. cit.; Jackson: Trans. Am. Acad. Ophtholmol. (reprint), 1921; Holinger et al.: Ann. Otol., Rhinol. and Laryngol., 59:547-564, June, 1950.

hood;[18] others believe it to be chiefly associated with middle age;[19] and yet a third group presents evidence that the symptoms of laryngeal papillomata may appear at any age, from birth to death.[20]

Statements about the mortality rate vary widely, too. The oft-quoted phrase, "always benign and usually self-limited," is liable to misinterpretation if taken out of context. Jackson and Jackson, probably first to use the expression,[21] hasten to add that neglect to remove the growths from the throat at proper intervals will endanger a child's life by reason of asphyxia. Ferguson and Scott use almost the same words quoted above, but go on to say that the condition is clinically treacherous, and cite fatalities. Bosworth, writing in 1892, did not consider the presence of "benign tumors of the larynx" any menace to life;[22a] Ward, writing more than half a century later, implied agreement with respect to adults only when he asserted that in the adult the growth, if completely removed does not recur and does not spread;[22b] however, this view does not seem to be widely shared at the present time. Diametrically opposed to such sanguinity is the writer who believes that in childhood papilloma of the larynx usually has a fatal outcome,[23] while others assert that in children under five years the mortality rate probably exceeds that of cancer of the larynx in the adult population.[24] Another writer reports two intractable cases in adults,[25] and still others boldly assert that papillomata may recur repeatedly after removal, at any age.[26]

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18. Green, loc. cit., says symptoms are most commonly noted about age two; Bradburn: The Laryngoscope, 51:1105-1113, Nov., 1951, says symptoms usually appear before age 5. See also opinion of Casuit, quoted by Roy, Ann. Otol., Rhinol. and Laryngol., 11:482-490, reprint, 1902.

19. Ingersoll: The Laryngoscope, reprint, August, 1898; also New and Erich, loc. cit., and Tebold quoted by Roy, loc. cit.

20. Jackson and Jackson, Diseases and Injuries of the Larynx on p. 361, report cases, age newborn to 84 years. Bosworth: A Treatise on Diseases of the Nose and Throat, Vol. II, pp. 718-720, refers to several congenital cases.

21. Op. cit., p. 362.

22a. Op. cit., p. 716.

22b. Ward and Hendrick: Diagnosis and Treatment of Tumors of Head and Neck, p. 596.

23. Zalin: Jour. Laryngol., Otol., 62:621-626, Oct., 1948, citing Holding, 1929.

24. Ferguson, loc. cit., and Zalin, loc. cit., both citing Crowe and Breitstein, 1922.

25. Cohen: South. Med. Jour., 26:621-625, July, 1933.

26. Equen: loc. cit.; also Amarante: A. M. A. Arch. Otolaryngol., 58:94-95, July, 1953.

As to the possibilities of malignant degeneration, we again find a disquieting lack of agreement. The *tendency* of papilloma of the larynx toward malignant change is variously said to be:

1. Non-existent in children;[27]
2. Rare at any age; probably only co-incidental;[28]
3. Present at all ages;[29]
4. Potential, in adults only;[30]
5. Always actively present in adults; the multiple type is a pre-cancerous lesion.[31]

This summation at least gives one a wide range of choice.

In view of the foregoing recital of differences in opinion, it is no surprise to find that methods of treatment have run the gamut from a "hands off" policy which admits the necessity for tracheotomy only in the event of acute respiratory distress, through a variety of local and systemic medications, to simple excision, radical surgery, X-radiation, radium, diathermy, or many and varied combinations of these procedures.

A normal shift in opinion and method of treatment, to conform with progress in science, fails to explain these strikingly antithetical conclusions, outlined above, for many of them have marched side-by-side, chronologically speaking. In studying the literature on this topic we no sooner feel that a generality has been established than we find report of an outstanding exception. How can we reconcile such divergencies? What is there in the character of this disease to explain its variety of seemingly contradictory forms of behavior? We are reminded of the ancient fable of the blind men and the elephant; the thought arises that perhaps our failure to understand the

27. Willis: Pathology of Tumors, p. 302, 1948; also Ferguson, loc. cit., and Zalin, loc. cit.

28. Babcock: loc. cit.

29. Cohen: loc. cit.; Figi: Minn. Med., 21:553-558, Aug., 1938; Ewing: Neoplastic Diseases, pp. 922-925.

30. Willis: op. cit., p. 302; Putney: A. M. A. Arch. Otolaryngol., 61:381-385, April, 1955.

31. Harris and Wattleworth: A. M. A. Arch. Otolaryngol., 53:640-645, June, 1951.

essential nature of laryngeal papilloma may explain the conflicts found in the various accounts of the disease.

This paper will review the theories of etiology and the principal methods of treatment of laryngeal papillomata and attempt to evacluate antibiotic therapy of the disease, with particular reference to aureomycin.

DEFINITION.

Stedman's Medical Dictionary, 18th edition (1953), defines papilloma as "A circumscribed overgrowth or hypertrophy of the papillae of a cutaneous or mucous surface; the papillomata include warts, condylomata, cutaneous horns, and various polypi."

It is generally agreed that laryngeal papilloma are benign papillary masses springing from a small base; may be single or multiple, and may occur in any part of the larynx.[32]

HISTOLOGY.

It is also generally agreed that papilloma arise from the squamous epithelium, that their cells are well differentiated, that they do not invade the stroma or extend below the basement membrane, and that their core consists of a rather vascular connective tissue. Lipschutz sometimes found inclusion bodies in the epithelial cells.[33]

Many investigators point out that while papillomata in children and in adults have identical characteristics, microscopically, yet their clinical behavior differs;[34] but as to the nature of that difference there is not complete accord. Broyles asserts that in adults the growths occur singly, and that while their complete removal results in a cure, the unoperated papilloma may become malignant. Amarante feels that, in the adult, papilloma is unpredictable; it may be cured by a single removal, or may recur repeatedly. Ward is convinced that in adults the completely removed papilloma does not recur and does not spread. Amarante expects recurrence during child-

32. Babcock: loc. cit.

33. Cited by Ferguson, loc. cit.

34. Broyles: Bull. Johns Hopkins Hosp., 66:319-322, May, 1940; also Boies: The Laryngoscope, 53:101-111, Feb., 1943; Ward and Hedrick: op. cit., pp. 596-597, 1950.

hood, but recommends removal only to facilitate respiration. Broyles expects multiple growths in children and implantation on adjacent sites; he does not find extirpation satisfactory in children. Both Amarante and Broyles anticipate disappearance of the growths at puberty, and in this Ward concurs.

GROSS APPEARANCE.

Seen through the laryngoscope, papillomata are characteristically mulberry-like masses with a nodular surface. They vary in size from the tiny, asymptomatic "millet seed" which is occasionally discovered incidentally or at autopsy, to fungating masses larger than an olive. They may project from the mucosa of the cords, the anterior commissure, or anywhere else; the anterior third of a vocal cord is a common site for these growths.

In color they range from grayish-pink or yellowish-pink to an angry red when engorged. In the latter state they have been thought to be less amenable to treatment.[35]

SYMPTOMS.

Symptoms of papilloma result from alterations of the laryngeal function which cause changes in respiration and phonation. Usually phonation is first affected; there is an alteration in the quality of the voice, followed by a hoarseness which progresses to complete aphonia. In the meantime the respiratory phase develops; there may be a croupy cough, followed by stridor and dyspnea which progresses to cyanosis and asphyxia, unless the course of the disease is reversed, either spontaneously or otherwise.

In children there may be obvious personality changes. Following the realization that they cannot play as others do, such children tend to become solitary, slow-moving figures, preferring reading or other sedentary occupation to any group activity. In acute cases there is a notable economy of motion as dyspnea increases; however, with the usual inconsistency of this disease, there are reports of cases which remained entirely asymptomatic. Ballinger cited one which resulted in

35. Ballinger: op. cit., p. 545.

death from asphyxia during a choking fit at the dinner table, without any prior manifestation.[36] In other instances, laryngeal papillomata have been first revealed at autopsy, after death from totally different causes.

Repeated upper respiratory infections, so frequently associated with laryngeal papilloma, are a characteristic result of interference with normal function. The child who has a series of "colds," and also demonstrates either hoarseness or an alteration in phonation, should be suspected of papilloma.

DIAGNOSIS.

Diagnosis is made by both indirect and direct laryngoscopy, and confirmed by histological examination of the removed tumor mass. In differential diagnosis the age of the patient helps decide which alternative diagnoses must be ruled out. In the adult one must consider the possibility of carcinoma, leukoplakia, hyperkeratosis, tuberculosis, and syphilis. With children one must think of congenital anomalies, such as webs and cysts, and of laryngeal stridor. Holinger states that polyps, vocal nodules, "screamer's nodes," and chronic laryngitis are common to both age groups, and these conditions, too, must be ruled out.

ETIOLOGY.

Chronic Irritation.

Probably the earliest theory of etiology which still has its adherents is that expressed by Bosworth in 1892,[37] and by Browne even earlier.[38] They believed that papilloma of the larynx is the result of chronic irritation. Browne traced more than half of a series of 26 cases to over-use of the voice. More convincingly, in a series of 300 cases Fauvel[39] found the greatest incidence among those whose work required special or excessive use of the voice, such as ministers.

While apparently accepting this theory of etiology, Bosworth also pointed out that not even a normal amount of func-

36. Ibid.
37. Op. cit., pp. 717-718.
38. Cited by Bosworth, op. cit., p. 717.
39. Ibid.

tional activity is necessary to produce the growth, and he cited Mackenzie's case of papilloma in the larynx of a deaf-mute.

Later Lennox Browne voiced the opinion that chronic nasal obstruction is an important "pre-disposing local cause" of papilloma.[40] With this Ingersoll agreed, as did Ballinger, some years later.[41]

Chronic Infection.

Shurly presented another theory.[42] He expressed the then current opinion of Mackenzie, Cohen, Semon, and Sajou by indicting "chronic laryngeal catarrh" as the "principal etiological factor" in producing papilloma. These men pointed to the almost constant respiratory infections present in many cases of papilloma, and interpreted that infection as the most probable cause of the growth, whereas more recent writers have concluded that such infection is more probably the *result* of the impaired respiratory drainage induced by the obstructing growths.[43]

The much earlier suspicion that lues is the antecedent of papilloma was discounted at the beginning of the Twentieth century. Mackenzie[44] went so far as to assert that both syphilis and tuberculosis "exercised an antagonistic influence on the development of new growths," including papillomas of the larynx, but Ballinger reasoned that any systemic infection would lower body resistance and thereby be more likely to pave the way for the development of papillomas.

Ballinger seems to have favored the theory of an infectious origin of the disease, specifying measles as an "exciting cause." Whatever influence he attributed to mouth breathing, or to other "local irritants," seems to have been on the basis of such an irritant preparing the soil for a more favorable growth of the responsible infection.

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40. Op. cit., pp. 650-657.

41. In 1911.

42. A Treatise on Diseases of the Nose and Throat, 2nd ed., pp. 564-565. 1905.

43. Rubin: loc. cit.

44. Cited by Ballinger, op. cit., p. 542.

Virus.

More recently we have observed the rise of a new theory: the hypothesis that a viral agent is the chief cause of laryngeal papilloma has been repeatedly tested and seems to be gaining acceptance.

Diseases now known to be caused by a virus were recognized hundreds of years ago, but their etiology was not suspected until a Russian scientist stumbled on a part of the mystery while studying the plant disease called "tobacco mosaic," in 1892.[45] He found that the infectious agent was in the juice of the plant,[46] and was filterable; but he failed to recognize the significance of his experiments, and it remained for the Dutch scientist, Beijernick, to realize that a new disease-producing agent, different from bacteria, had been discovered.

During the past decade, viruses have been subjected to much careful research. Many earlier concepts are now being discarded, while others are under scrutiny; but certain outstanding characteristics of viruses appear to be verified.

From our point of view, the most important of these are:[47]

1. Viruses are able to pass through filters which hold back the smallest known bacteria.

2. Viruses are parasites at the cellular level.

3. Viruses are able to multiply with astonishing rapidity, but only within the living cells of certain susceptible hosts.

The most generally accepted criterion of a virus is that it can be transmitted by a cell-free filtrate.[48]

The first recognized virus disease of animals was foot and mouth disease. Soon it was proved that a virus causes certain types of tumorous growths in fowl, and later this same agent

45. Stanley: Recent Advances in the Study of Viruses, Science in Progress, ed. by Rivers, First Series, pp. 78-111.

46. Cf. observations of Hubbard, Boies, and Kirchner, referred to in this ms., p. 15.

47. Burrows et al.: Textbook of Microbiology 16th ed., pp. 713-735. Frobisher: Fundamentals of Microbiology, 5th ed., pp. 61-64. Stanley: loc. cit., pp. 80-83. Greenstein and Haddow: Advances in Cancer Research, Vol. II, 1954, p. 405.

48. Burrows: op. cit., p. 715.

was demonstrated to cause some forms of growths in animals as well.

As early as 1891 it was observed that contact with the cut surface of a common wart on the hand produced similar lesions on the contacting skin.[49] Experiments made by Variot in 1893, and by Judassohn in 1894, supported the hypothesis that some agent in the blood from verruca was capable of transmitting the growth from one host to another. Encouraged by these observations, Udo J. Wile made a series of experiments from which he concluded that warts can be produced by a virus which will pass through a Berkefeld filter.[50]

It had long been suspected that papilloma of the larynx, genital warts, and common verruca are all manifestations of the same pathological phenomenon, for as early as 1853 Buck had noted their similarity.[51] This suspicion was given strong support in 1923 when Ullman successfully innoculated the vaginal membrane of a dog with laryngeal papilloma, using bacteria-free filtrate.[52] His experiment simultaneously presented convincing evidence that genital warts and laryngeal papilloma are of the same etiology, and that a virus is responsible for both.

In the meantime, Hubbard[53] noted evidence of contact reproduction in "warts, bladder polyps, and laryngeal papillomas." He pleaded for extreme care and gentleness in the handling of these growths warning strongly that "the very juices of the neoplasm may be the agency of transplantation."

Boies,[54] favoring the viral theory, added, "It has been my clinical impression that the rapid appearance of papilloma in the trachea of a small child after scalping off multiple laryngeal growths was probably the result of expressing secretion from these growths in my efforts at removal."

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49. Wile and Kingery: J. A. M. A., 73:970-972, Sept. 27. 1919.

50. Ibid. Also, Warren: Warts; Verrucae, Viral and Rickettsial Infections of Man, 2nd ed., ed. by Rivers, p. 669.

51. Trans. Amer. Med. Assoc. (reprint), 6:510-535, 1853.

52. Boies: loc. cit.

53. Hubbard and Galbraith: Arch. Otolaryngol., 1:70-78, Jan., 1925.

54. Writing in 1943.

Eight years later Kirchner[55] voiced a similar thought, saying that trauma, "even sponging with gauze," seemed to spread the growth. He observed that the majority of extensions were found along the line of previous instrumentation.

Ferguson, reporting on his series of cases in the following year, admitted that a filterable virus might be a cause of papilloma but felt that not enough evidence had yet been presented to prove the point beyond dispute.

Zalin, writing a few years later,[56] accepted the virus theory and advanced the hypothesis of antibody immunity to account for spontaneous remission before puberty. With respect to that regression of the growths which has so often been observed at puberty, he suggested, "it is highly possible that the mature epithelium presents a barrier to virus activity not present in the immature tissue."[57]

As more became known about the behavior of viruses, the theory of viral etiology gained adherents. Holinger accepted it, modified by a recognition of the probable influence of hormones, much in the manner expressed by Zalin, and based a new therapeutic regimen upon that assumption.[58]

By 1952, Joel Warren was able to assert: "It has been definitely shown that an agent filterable through Berkefeld candles of all grades of porosity is responsible for warts. . . . Furthermore, most workers believe that a single etiological agent is responsible for the different types of warts mentioned."[59] In his list of warts, Warren specifically includes laryngeal papilloma; we are reminded of that ancient description, "warts in the throat."[60]

Green agreed with Holinger as to etiology, and reported a case[61] treated successfully by Holinger's method. By 1954 Rubin[62] felt justified in stating that the viral theory of etiology is now favored by the majority of authors.

55. Laryngoscope, 61:1022-1029, Oct., 1951.
56. In 1948.
57. See discussion under Medical Treatment, this ms., p. 25.
58. His theories and methods are discussed in this ms., p. 28.
59. Warts: Verruca, in Viral and Rickettsial Infections of Man, edited by Thomas M. Rivers, 2nd ed., p. 669.
60. This ms., p. 1.
61. Loc. cit., 1953.
62. Loc. cit.

FORMS OF TREATMENT.

Before the invention of the laryngoscope, any recognizable papilloma probably was of considerable size and required heroic measures. Removal usually was accomplished through an incision made in the neck, though Bosworth reports that at least four workers had successfully removed laryngeal papilloma through the mouth, prior to 1892. More commonly, tracheotomy alone was done, and that only when respiration became greatly embarrassed. There were so many early instances of spontaneous regression of the growth that Ballinger wrote, in 1911, "Like warts on the skin, papillomata of the larynx come and go without any apparent reason."[63] This characteristic of the disease may explain why so many different forms of treatment have been inaugurated, used successfully by one or two men, and then tried without benefit by later workers. It also makes the evaluation of any form of treatment extraordinarily difficult.

Since various combinations of methods have been used, we shall consider treatment under the headings of Surgical, Physical, and Medical, according to the type which predominates in a given regimen of therapy.

Surgical.

From ancient times, when purely mechanical limitations may have dictated the method of treatment, tracheotomy has been a favorite procedure, not only as an emergency measure but also as a primary treatment for laryngeal papilloma. Roy early (1902) expressed a conviction that voice rest, obtained by tracheotomy, provided the best possible therapy, particularly in children. Brose, as well as other of Roy's contemporaries, agreed with that view, as do such modern writers as Zalin (1948), Ward (1950), Gorrell,[64] and Amarante (1953).

On the other hand, New,[65] McKinney,[66] and Ferguson (1944) saw no benefit in tracheotomy save as a temporary emergency measure. The hazards of dependence on trache-

63. Op. cit., p. 545.

64. Canad. Med. Assoc. Jour., 67:425-427, Nov., 1952.

65. Ann. Otol. Rhinol. and Laryngol., 30:631-636, Sept., 1921. He mentions a woman age 22, whose larynx was filled with papilloma and who had worn a tracheotomy tube since age 2.

66. Memphis Med. Monthly., reprint, Sept., 1915.

otomy as a routine therapy have been pointed out. *First*, sole reliance on tracheotomy may mask extensions of the disease which are incompatible with life, as in the case reported by Kirchner.[67] *Second*, unless the patient is closely and continuously supervised by a competent person, the tracheotomy cannula may become clogged or dislodged, or asphyxia may result from clumsy attempts to change the cannula at home. Deaths from such causes have been reported by Hitz,[68] Gorrell,[69] Buck,[70] and others. *Third*, malignant degeneration may take place undetected, as in the two fatal cases reported by Walsh.[71] One child wore a tracheotomy tube continuously from the age of 34 months until death from unsuspected malignancy at the age of 12; the other patient had continuous tracheotomy from age 3 until death from malignancy at age 11.

Forceps removal, repeated as often as necessary, probably has more adherents than any other method of treatment. Brose[72] recommended endolaryngeal removal in conjunction with tracheotomy. Jackson[73] reminded us that the disease is "self-limiting" in children, and predicted recurrences until the "time limit" is reached, no matter what form of treatment is employed; therefore, he recommended scalping off the projecting parts as often as is necessary to maintain an adequate airway, enjoining care that the normal tissues be not injured. Cohen[74] felt that surgical extirpation is the best method for adults as well as for children, asserting that a single procedure often suffices, but that two or more sittings may be required if the growth be multiple. Babcock[75] agreed. Broyles[76] felt that endoscopic removal is best at all times for adults, but effective for children only if accomplished during a period of either quiescence or regression, as determined by observation. Equen[77] preferred removal "flush with the surface" for children. Ferguson[78] thoroughly agreed with Jackson.

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67. loc. cit.

68. Am. Jour. Path. (reprint), 8:333-338, 1938.

69. loc. cit., 1952.

70. loc. cit., 1853.

71. Laryngoscope, 60:1110-1124, Nov., 1950.

72. Paper published in 1905; the following dates are given to show continuity: 73. Paper published in 1921; 74. Paper published in 1933; 75. Paper published in 1934; 76. Paper published in 1941; 77. Paper published in 1941; 78. Paper published in 1944; 79. Paper published in 1951; 80. Paper published in 1954.

Harris[79] reviewed 116 cases, some treated by surgery and some by X-ray, and concluded that in the groups under his observation, surgery had given the better result. Rubin[80] stated that the treatment of choice, at any age, is forceps removal, repeated as often as necessary. The most recent opinion we have seen, that of Putney, published in 1955, expressed strong preference for surgical removal alone, mainly because such procedure permits repeated examination by the pathologist throughout the course of the disease, which this author regards as always potentially malignant.

To present just one opinion on the opposite side, we note that Hollingsworth[81] objected a few years ago that surgical removal requires "long hospitalization and repeated instrumentation," and advocated instead a form of medical treatment, which will be discussed later.

Physical Treatment.

In 1921, New reported on a series of 26 children seen at Mayo's over a period of six years. These patients, many of whom had repeated surgical excisions and/or tracheotomies previously, were treated with radium, under general anesthetic, using the Lynch suspension apparatus. These treatments, given at intervals of six to eight weeks, varied in number from one to six, and were sometimes supplemented with external radium. The patients ranged in age from 10 months to 12 years. He discounted nine cases for various reasons,[82] found improvement in six who still required further treatment, and reported a clear larynx in 11 of the group. The exact length of follow-up at the time of the report is not specified. This author found none of the previously deplored complications attendant upon radiation therapy; however, it is interesting to note that in a paper presented some years later, in 1938, he expressed a preference for diathermy.

Foster,[83] while insisting upon the necessity for tracheotomy in every case, recommended careful X-radiation as an adjunct, specifying that the "improved methods" of X-ray be used. His

81. Hollingsworth et al.: Arch. Otolaryngol., 52:82-87, July, 1950.

82. One died after emergency tracheotomy, one died at home for want of tracheotomy, four did not complete the course of treatment, two were "unable to return," and one was lost to follow-up.

83. South. Med. Jour., 26:625-630, July, 1933.

report was concerned primarily with children, but about the same time Cohen also expressed approval of X-ray after surgery for adults, if done with great care, though he preferred excision alone for both age groups.

About ten years later, Salinger[84] condemned irradiation as "dangerous to children and valueless to adults;" he reported arrested development of the larynx of a child following irradiation. He considered such a result an inherent danger of irradiation, and concluded that the procedure had already been generally discarded.

Diathermy was advocated by Hubbard as early as 1925, and 13 years later by New and Erich. These men felt that "the juices of the neoplasm" were a means of its spread, and hence preferred a bloodless method of treatment. Their reasoning was based on the same observations which later led to annunciation of the viral theory of etiology.[85]

Medical Treatment.

Attempts at medical methods of conquering laryngeal papilloma began at a fairly early date. Delevan,[86] Roy,[87] Kyle,[88] and Stuckey[89] independently reported success in the treatment of adult cases from local applications of alcohol, usually in conjunction with tracheotomy; but others used this method without benefit. Though approving alcohol, Roy expressed belief that the voice rest provided by the concomitant tracheotomy was the better part of the therapy. This author also noted spontaneous cure in a 9-year-old girl after surgery was unavoidably delayed; her only treatment was repeated swabbings with cocaine, to which he attributed no curative power.

Shurly[90] is reported to have used Thuja Occidentalis with good results; Ballinger recommended arsenic as the best of

84. Ann. Otol., Rhinol. and Laryngol., 51:273-277, March, 1942.

85. See this ms., p. 15 ff.

86. Cited by Ballinger, op. cit., p. 544; strength not given.

87. loc. cit., 1902; daily applications, strength not specified, were followed by regression of growths; no details.

88. A Textbook of Diseases of the Nose and Throat, 4th ed., 1907, pp. 221-224. He reported "injections of pure alcohol into these benign growths are highly beneficial."

89. Tr. Am. Laryngol., Rhinol. and Otol. Society (reprint), 1913. He recommended alcohol of increasing strength daily, indefinitely.

90. Cited by Ballinger, op. cit., p. 544.

internal remedies, but gave no details. Katz[91] advised local applications of magnesium oxide after excision, to discourage regrowth. A variety of other local medications are mentioned in the literature, but none seems to have gained a wide or lasting acceptance. The search for a more effective treatment continued.

In the meantime, the observation that the papilloma of childhood tended to disappear at puberty gave rise to a theory of hormonal relationship, and pointed the way to experiments with estrogens to ameliorate and/or reverse the course of the disease in children.

Te Linde and Brawner[92] had demonstrated that the vaginal mucosa of young girls could be quickly altered from the simple, infantile type to the stratified adult type of squamous epithelium, thereby making it more resistant to infection.

The question then arose, since papilloma of the larynx tends to disappear at puberty, would a forced change to adult type epithelium hasten this disappearance? Turning to the hormones, Holt[93] experimented unsuccessfully with testosterone; in his subjects, secondary sex characteristics immediately appeared, but the papillomata were not affected.

Broyles then began treatment of five patients with estrogen, resorting to surgical removal of the growths as necessary. His patients in this series were 5 to 7 years old, and all had been previously treated elsewhere, usually by repeated surgical removal. In each instance, Broyles[94] was able to report a normal voice and a clear larynx within periods ranging from two months to one year after the first of a weekly series of applications of Amniotin. Four of these patients had been followed for approximately one year at the time of his report, and no return of symptoms had been observed; but in 1944, Ferguson reported a trial of Amniotin on a single case with no success. It is not known whether or not the dosage and duration of treatment were identical with those employed by Broyles.

91. Cited by New and Erich, 1938.
92. Am. Jour. Obst. and Gynec., 30:512-523, Oct., 1935.
93. Cited by Broyles in 1940.
94. Paper published in 1940.

In 1948, Zalin reported treatment of three patients with Organon, supplemented in one instance with Stilbestrol. He felt that this method was successful, in that the lumen was cleared by the treatment, and in two cases remained clear for the three-year period up to the time of his report; the third case was still under treatment.

Ward, in 1950, reported that local applications of Amniotin seemed to hasten the change from infantile to adult type epithelium, and that once such a change was accomplished the growth could be completely excised without fear of recurrence. In this there is an echo of the earlier observation that in children the surgical extirpation of papillomata is not successful unless the growths have reached a stage of quiescence or regression.

Opposed to those who found hormonal therapy effective, Hollingsworth[95] noted that Amniotin had been used without relief in one of the cases which came to his attention, and as recently as 1953, Amarante regarded hormonal treatment as wholly unsuccessful.

In the meantime, Hollingsworth and associates had begun to study the problem from the viewpoint of comparative histology. They remarked upon a previously-discovered similarity between venereal papilloma (verruca acuminata) and laryngeal papilloma, both in histologic appearance and in tendency to recur.[96] They appear to have disregarded the earlier work of Ullman and of Wile, though the conclusions of both tended to support Hollingsworth's theory. Noting that venereal papillomata had been treated successfully with resin of podophyllum,[97] they began experimenting in the treatment of laryngeal papilloma with the same preparation, which is said to have the property of arresting mitosis. These workers also observed that it immediately caused neoplastic tissue to turn gray in color.

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95. Paper published in 1950.

96. Eggleston and Wolff: Histopathology of the Ear, Nose, and Throat, 1947, cited by Hollingsworth.

97. I. W. Kaplan: Condylomata Acuminata: New Orleans Med. and Surg. Jour., 94:388-390, Feb., 1942, cited by Hollingsworth and not included in the appended bibliography.

Reporting on a series of five cases, each of which had been subjected to various other prior treatments[98] without improvement, Hollingsworth concluded that repeated weekly topical applications of a 10 to 15 per cent solution of podophyllum in 95 per cent alcohol, over a period of several weeks, resulted in regression, if not total disappearance, of the papilloma. After the first three or four treatments he lengthened the interval between treatments, as the situation indicated. He also removed the growths surgically as often as seemed necessary and found that the continued use of podophyllum progressively facilitated subsequent removals. It is interesting to note his comment on the use of antibiotics: "prolonged courses of treatment with penicillin, streptomycin, and Aureomycin apparently have no effect in inhibiting the growth of laryngeal papilloma."

Hollingsworth's criticism serves as a back-handed introduction to the most recent form of medical treatment, the antibiotics.

The use of antibiotics in treatment of laryngeal papilloma was the inevitable result of increasing interest in the viral theory of etiology. When the specificity of Aureomycin for certain virus infections had been demonstrated, Holinger[99] was probably first to report its successful application to papilloma of the larynx. In 1950 he reviewed a series of seven cases which he had found amenable to Aureomycin. This he had administered in dosages of 25 to 50 mm. per kilogram of body weight, depending upon the individual condition, over periods of from two to four weeks, following excision; in three instances he gave a second course of Aureomycin over a three-week period. The results were encouraging, and he remarked that the larynx appeared smoother than when surgery alone was used. Because of the small number involved and the comparatively brief span of time which had elapsed since treatment, he felt that it was too early to draw firm conclusions at the time of his first report. A year later he was able to add

98. Prior treatments in each of the five cases were: a. Surgical excision and tracheotomy; Amniotin spray, but strength, frequency, and duration of treatment not specified. b. Aureomycin, sulfadiazine, and penicillin for associated septicemia, given over 16-day period; unspecified dosage. c. Tracheotomy and Amniotin, unspecified dose; repeated courses of penicillin and streptomycin for recurrent respiratory infection; unspecified dosage; d. Surgical removal, twice. e. Surgical removal; repeated tracheotomy; radiation; hormonal therapy, no details.

99. loc. cit., 1950.

two more cases to his list of those successfully treated and to bring the previously-treated cases up to date.[100] In three of the first group he had obtained a clear larynx, and there was obvious regression of the growths in the remaining four.

A few followed Hollinger's lead at once. Green[101] soon reported a case in which use of Aureomycin brought about a dramatic disappearance of the papillomata in the larynx of a 3-year-old boy. The child had previously required many removals of the growth, and repeated tracheotomies. Finally he was given 200 milligrams of Aureomycin every six hours over a period of ten days. Regression of the growths was apparent within a few days, and at the end of three weeks his larynx appeared entirely free of papillomata on direct laryngoscopy. He had been followed for two years at the time of the report, was in good health, with good voice, and a larynx which still appeared "perfectly clear."

McCart[102] reported the case of a boy, age 10, who suffered from dyspnea and required immediate tracheotomy. He had manifested symptoms of laryngeal papilloma for three years and had been treated with radium beams elsewhere. He was now given a course of Aureomycin,[103] which brought about relief of his symptoms and seeming regression in the growths; but within a few months he was readmitted with evidence of malignant degeneration, and soon died of massive pulmonary hemorrhage.

Shortly after Holinger's first report on his results from Aureomycin, Bradburn[104] published an account of the successful treatment of four patients with Terramycin. This group was comprised of three children and one adult, and had previously been treated elsewhere. After excision of the growths, Bradburn administered Terramycin, in doses of 50 mgm. per kilogram of body weight, daily for two months or more. In all four cases he found the response to be both immediate and gratifying, but at the time of his report, no case had yet been followed for more than six months.

100. Ann. Otol., Rhinol. and Laryngol., 60:496 (reprint), June, 1951.
101. loc. cit., paper published in 1953.
102. Ann. Otol., Rhinol. and Laryngol., 63:498-499, June, 1954.
103. Dosage not specified.
104. loc. cit., paper published in 1955.

Opposed to these instances of successful treatment with antibiotics is Putney's conclusion that any improvement which has seemed to result from antibiotic therapy has in reality been due to the elimination of co-existing infection, and not to any successful attack upon the growth itself.

DISCUSSION.

Other observers have already commented that the continuing variety of treatments offered laryngeal papilloma indicates that the most effective method has not yet been found. It is amazing that so many workers have reported success with a given form of treatment, only to have later writers condemn it as unsound or ineffectual, a sequence of events many times repeated in the literature of this disease.

Possible explanations for this rather strange situation occur to the reader:

1. In some instances, the beginning of the treatment may have roughly coincided with the regressive phase of the disease, as suggested by Jackson in his paper of 1921.

2. While clinical manifestations and gross appearance of the growths are essentially the same, there may exist unsuspected differences in etiology which account for the variations in response to treatment. Even assuming that all laryngeal papillomata are of viral etiology, there is yet room for difference in the particular virus responsible in each of several different cases, particularly in different age groups, and probably even within the same age group. As investigation progresses, it becomes more and more apparent that the viruses offer an unexpectedly wide field for study and that their uninhibited behavior, their response to medication, and even their size is subject to infinite variety.

3. Over the years, and perhaps even at the present time, there have been some differences in pathological nomenclature. This is of especial importance in accounting for differences of opinion as to tendency toward malignant degeneration.

4. In view of the comparatively low and now declining incidence of the disease, no one worker has had opportunity of

105. loc. cit., 1955.

observing response to a single therapeutic regimen in a large series of cases of any one age group. This has inevitably led to the formation of at least tentative conclusions on slighter evidence than is usually considered desirable; therefore we have of necessity approached the problem of treatment in a somewhat empirical manner.

Etiology.

The bulk of present evidence appears to favor the theory of viral etiology; however, we are reminded that this does not instantly provide a specific form of control, but rather opens the way to a new field of speculation and a comparatively unexplored method of treatment. In a sense we do not "know" nearly so much about viruses and their responses today as we did a few years ago, and perhaps our most important recent advance is a realization of this very lack of knowledge.

Incidence of the disease appears to be declining rapidly. Cunning postulates that improved nutrition is the principal cause, since the lower rate was apparent before common use of the antibiotics. If his hypothesis be true, it might be regarded as another bit of evidence to support the viral theory of etiology, since adequately nourished tissue would seem less liable to infection.

Varied Response to Antibiotic Therapy.

In reviewing the literature it appears that in instances where treatment with antibiotics has been followed by an obvious and continued regression of symptoms, or by complete disappearance of the papillomata, the dosage has been both massive and long-continued, by conventional standards. In the available reports of cases where the antibiotics have been found disappointing, the strength and extent of dosage has often not been specified, but we strongly suspect, from our own observation, that it has been uniformly inadequate.

In five cases which have come to our personal attention it appears that only massive doses have an inhibiting effect on the growths, and that lasting benefit results only if the medication is continued over a comparatively long period of time; a period of weeks, rather than hours, of months rather than days.

To illustrate, note that in Case I of the appended series of Case Reports, when conventional doses of antibiotic were given there was no appreciable change in the frequency with which the larynx refilled with growths; when the dosage was increased by 50 per cent the intervals between surgery were doubled; treatment with massive doses of Aureomycin over a period of weeks was followed by an immediate regression of symptoms and obviated the need for further surgery. The age of this patient, 53 years when first seen, discounts any possible hormonal influence.

In Case Report II, note that conventional doses of Duracillin in a 19-months-old boy had no appreciable effect on the papillomata, but massive doses of Aureomycin brought about almost immediate diminution of the growths.

In Case Report III, the patient's history included numerous attempts at removal, each of which resulted in regrowth. After one course of massive Aureomycin therapy there was a regression and an eventual disappearance of the papillomata. Thereafter the difficulty arose from the considerable amount of scar itssue which had accumulated over the years because of the repeated surgery, a result which argues well for the need to eliminate as many surgical procedures as can be omitted with safety, and to safeguard normal tissue as much as possible.

In Case Report IV, we find that it had been necessary to remove the growths at intervals of decreasing length until massive Duracillin therapy was begun. The next interval was three times the length of the greatest previous period between surgical procedures, but the growths still returned. Then massive Aureomycin therapy was instituted, and within 30 days the papillomata had definitely diminished in both number and size. The patient at that time was 3 years old. Aureomycin was continued and repeated laryngoscopic examinations verified the regression of the growths over a period of one year. At that time the cords appeared more smooth than is usually the case when only surgery is employed.

Case Report V shows much the same picture. When first seen, this 2-year-old child presented a glottis well filled with papillomata. After extirpation of the growths, massive doses

of Duracillin were given for only three days. A diminution of symptoms resulted, so that the intervals between surgery were lengthened; but when massive Aureomycin therapy was begun, approximately a year after the patient was first seen, there was an almost immediate disappearance of symptoms, and after three months of Aureomycin, no papillomata could be seen on direct laryngoscopy.

Observations of only these five cases obviously cannot be offered as conclusive evidence of the efficacy of Aureomycin in the treatment of laryngeal papilloma; however, it will be remembered that in each of these cases an obvious regression of symptoms began only after massive doses of antibiotics, and that continued relief resulted only after massive doses of Aureomycin over a considerable length of time. In none of these cases could puberty have been a factor. Nor have other cases of the same age groups followed this same pattern of response, in our experience, when treated by either surgery alone or by surgery supplemented in any other manner.

A profile of 15 additional unpublished cases, treated at a University Hospital with varying amounts of antibiotics, is appended to demonstrate further the need for massive and prolonged medication, if these drugs are to be effective.

It is probable that in the past some of the discouraging reports on antibiotic therapy have resulted from judging its incidental effect, or rather lack of effect, on laryngeal papillomata when the medication was administered in the conventional amount, for the conventional length of time, in the specific treatment of an associated infection. Others have stemmed from an underestimate of the dosage necessary to control the disease while remaining within the limits of human tolerance.

CONCLUSIONS.

1. Present evidence indicates that laryngeal papilloma is of viral etiology.

2. Adequate dosages of antibiotics tend to control the disease.

3. It is the experience and observation of the writer that a sufficient dosage of Aureomycin, administered over a period of months, effectively supplements the surgical removal of stubborn papillomata and results in a clearer larynx than that usually achieved by means of surgery alone.

CASE REPORTS.

The following five cases, with diagnosis of laryngeal papilloma verified by histologic examination, have been under observation for five years or longer and have been treated with Aureomycin by either the writer or a colleague:

Case 1: C. H., a white woman, age 53 when first seen by a colleague in January of 1945. She complained of loss of voice, attributing her condition to the extraction of four teeth the preceding June, and asserting that she had experienced constant "throat trouble" since then.

First examination revealed greatly enlarged and seriously infected tonsils; accordingly, tonsillectomy was done. A very small papillomatous growth was observed on the left true cord, but was not removed at this time.

Five weeks later she returned to the office, again complaining of loss of voice. At this time, examination revealed growths on the left vocal cord extending from the anterior third up to the commissure. Biting forceps were used under direct laryngoscopy to remove all the extraneous tissue. A specimen sent to the laboratory was reported "fibro-epithelial papilloma with branching stalks of connective tissue covered with heavy layers of stratified squamous epithelium." Following this surgical procedure there was considerable improvement in the patient's voice.

Approximately eight months later she returned to the office, again unable to talk. She was readmitted to the hospital on Nov. 19, 1945, and this time a papilloma the size of a glass pin head was found at the junction of the anterior and the middle third of the left cord. This was removed with biting forceps, and the anterior two-thirds of each vocal cord, as well as the ventricular bands, were cleaned as well as possible with the forceps. The pathological report was again "benign papilloma." Improvement in voice again resulted, but only temporarily.

In May of 1946 she returned, again complaining of loss of voice. On May 21, multiple papillomata were removed, and again the voice improved.

In November of that year she again became unable to speak aloud. At that time, papillomata were found to cover the anterior two-thirds of the cords on both sides. The growths were removed by forceps on Nov. 22, and at this time considerable bleeding was encountered. Penicillin, 20,000 units every four hours, was given for three days, beginning Nov. 24.

She was re-hospitalized on May 12, 1947, with complete loss of voice. On this admission, growths were found on each vocal cord, the ventricular bands, and the anterior commissure. Small cup forceps were used to exenterate the papillomata from the entire glottis. Following this procedure, penicillin, 30,000 units every four hours, was begun May 16 and continued for one week.

The next hospital admission was March 9, 1948, again with total loss of voice. Growths were removed from both cords on March 10, and then superficial coagulation was done. Penicillin, 40,000 units every four hours, was given for one week.

Following this treatment the usual improvement lasted more than a year, but on May 4, 1949, the patient was again admitted, with not only total loss of voice but dyspnea as well. It was found that the vocal cords were again covered with papillomata, which were removed under direct laryngoscopy on May 5. Penicillin was repeated, as on the last admission.

This patient was not seen again until Oct. 22, 1950, when papillomata were again removed, as before. Penicillin was repeated, as previously.

On Dec. 12, 1951, the patient returned and presented a larynx fairly well filled with papillomata. The following day the growths were again removed. Aureomycin, 250 milligrams every six hours, was begun and continued for three weeks.

Approximately a year later the patient was again hospitalized, but this time for posterior myocardial infarction. She was able to speak only in a whisper, but the larynx appeared reasonably clear, despite the numerous surgical procedures. She has not required further treatment for the papillomata, up to August of 1955.

Case 2: H. L. G., a white boy, age 19 months when first seen by a colleague Dec. 15, 1948. His parents reported continued hoarseness and difficult breathing since birth; he suffered from repeated upper respiratory infections. There had been an exacerbation of symptoms following a recent acute bout of such infection. Examination revealed multiple papillomata. These were removed Dec. 16, diagnosis confirmed by pathologic examination, and Duracillin was given, 1 cc. daily for five days. Immediate improvement was noted following surgery.

He returned to the office in seven months, with hoarseness and dyspnea, aggravated by recent upper respiratory infection. On Aug. 1, 1949, multiple papillomas were removed and Duracillin was given, as before.

Because of dyspnea it again became necessary to remove the papillomata on Jan. 12, 1950. At that time the larynx appeared to be completely filled with the growths. Duracillin was given, as before.

The symptoms recurred and the treatment was repeated seven times up to April of 1951. At that time the larynx was covered with papillomata, from the ventricular folds on down into the trachea, and the airway was very poor. Large amounts of papillomatous tissue were removed, piecemeal, from both sides, thereby improving the airway. Aureomycin therapy was then instituted, 100 milligrams every three hours for the first three days, and twice each day thereafter for a period of nine weeks. During this period of treatment the larynx was twice inspected and showed progressive improvement. No surgical intervention was necessary for eleven months.

By May of 1952, dyspnea had returned and it became necessary to remove the papillomata. No more Aureomycin was given.

Surgical removal of the growths was necessary again in February of 1953.

The child was last seen when the growths were removed again May 7, 1953. At that time, multiple papillomata were found, chiefly on the left side: the superior surface of the left cord, the anterior two-thirds of the left cord, and only the posterior surface of the right cord were involved. This represented considerable improvement over some of the

previous admissions, but indicated a trend toward another series of required surgical procedures of increasing frequency.

Case 3: R. J. O., a white boy, age 6 years when first seen by a colleague February, 1950. He was hospitalized Feb. 2, unable to speak above a whisper. He had a history of many previous hospitalizations for laryngeal papilloma, and a permanent tracheotomy since the age of 2. At the time of this admission he had little or no airway. Laryngoscopic examination revealed severe fibrosis and multiple papilloma. No surgery was attempted.

Three months later he was re-admitted and much of the growth was removed with bent cup forceps. He was then given a six-weeks' course of Aureomycin, 150 mgm. twice each day.

Seven months later, in December, he was re-admitted because of laryngeal stenosis. On examination he was found to be free of papilloma, but there was much scar tissue. The family was transferred elsewhere and the patient was not seen again.

Case 4: L. G. S., a white boy, age 2 when first seen, Oct. 21, 1948, complaining of "difficult breathing" for the past month. There had been a sudden onset of hoarseness in February, and this seemed to be increasing somewhat. Direct larygoscopy, done the following day, revealed multiple papilloma on the right cord, extending to the anterior commissure; diagnosis confirmed by biopsy. The growths were removed and the voice improved.

The child became hoarse and dyspnea returned. Papilloma were removed Feb. 27, 1949, and again on March 11, because of recurrent dyspnea. At this time both cords were covered.

Continued difficulty in breathing was relieved by a tracheotomy done March 29, 1949. He was closely followed and the tube was changed every four or five days at the office until late Summer of 1950.

On Aug. 22, 1950, multiple papillomata were removed under direct laryngoscopy, and Aureomycin therapy was begun.

Aureomycin Spersoids, 4 cc. every three hours, given in milk, was continued after the patient was dismissed from the hospital. The next examination, Sept. 19, revealed smaller and less numerous growths, a moderate improvement. The child was again closely followed, returning to the office for changes of the tracheotomy tube, as before.

By Jan. 23, 1951, laryngoscopy revealed considerable improvement. One papilloma was removed from the left cord, two from the right. Aureomycin therapy was continued.

On May 8, 1951, direct laryngoscopy showed only a small nodule on the posterior end of the right true cord. The left cord was thickened; both moved readily with respiration. On Sept. 18, 1951, a single residual papilloma was removed and the tracheotomy stoma was closed. The pathology report was essentially the same as the one made after the first removal of the growths. Aureomycin was now discontinued.

By Sept. 26, 1951, mirror examination revealed a good airway. The child had begun to talk in whispers. In another ten days he was talking very well. He was examined by mirror at frequent intervals, and by direct laryngoscopy on Feb. 29, 1952. At that time both true cords were smooth and the airway appeared good. No papilloma could be seen.

He has since been seen at intervals of approximately six months, the last office visit being May 23, 1955. At that time his voice was good; he had no hoarseness for the past three years. Mirror examination revealed both true cords to be pearly white, with free edges and superior surface entirely smooth. There was no evidence of recurrent papilloma.

This patient had been on Aureomycin continuously for 13 months. He was 9 years old when last seen.

Case 5: L. C. M., a white girl, age 22 months when first seen, Sept. 3, 1948. She had no voice since an episode of measles, five months previously.

Direct laryngoscopy was done Sept. 9, 1948, and revealed a small growth on the left vocal cord. This was removed on Nov. 12, 1948, and proved to be papilloma. The voice then returned.

She was seen again on Feb. 3, 1949; the voice was much better at that time; however, by May she had developed considerable hoarseness. Soon thereafter she had pertussis, so that laryngeal treatment was postponed until Sept. 16. At that time a direct laryngoscopy revealed a very poor air way and a paralyzed right vocal cord. Tracheotomy was done the following day. Thereafter she was kept under close supervision. The papillomata returned, covering both vocal cords, and were removed, as well as possible, on June 9, 1950, under direct laryngoscopy. On Aug. 28, 1950, we began the administration of Aureomycin Spersoids, 4 cc. every three hours, and on Sept. 19, papillomata were again removed from the anterior third of both true cords.

The next examination showed marked improvement. She was examined by mirror at regular intervals until Feb. 6, 1951, when direct laryngoscopy revealed a narrowed glottic chink but an adequate airway, without any evidence of papilloma. In the meantime, the voice had improved and continued to do so.

On April 17, 1951, direct laryngoscopy showed a small papilloma on the left cord. This was promptly removed.

Regular examination indicated progressive improvement, and on Sept. 25, 1951, the tracheal stoma was closed.

On Feb. 25, 1952, no papilloma could be seen, and the voice was good.

By Jan. 19, 1953, one small papilloma had appeared on the epiglottis, and there was appreciable hoarseness.

On June 16, 1953, a papilloma was removed from the anterior portion of the right vocal cord and another from the posterior portion of the left cord. Since that time repeated mirror examinations have failed to disclose any further return of papilloma. Aureomycin was discontinued in April, 1954, after slightly more than three years of medication.

When last seen, in February of 1955, the voice was strong, the true cords were pearly white and smooth, and breathing was normal.

CASE PROFILES.

The cases reported in the following profiles were treated for laryngeal papilloma at the State University of Iowa Hospital, Department of Otolaryngology and Oral Surgery, and permission was given by that Department to abstract the necessary information from their records.

In each instance, the diagnosis was confirmed by pathologist's report.

Ages and methods of treatment in this series vary, as does length of follow-up. In one or two of these cases the patient was lost to follow-up before there was sufficient time for any evaluation of the results of treatment.

The sole criterion for selection of these particular cases was that each patient received at least one course of antibiotics, no matter how brief. The purpose is to show the response of laryngeal papilloma to antibiotic therapy of varying dosage and duration. We are particularly concerned with degree of response in relation to amount of dose, and duration of response in relation to duration of the medication.

We feel that these profiles further demonstrate our conviction that massive and long-continued antibiotic therapy, with Aureomycin in particular, effectively supplements surgery in the treatment of laryngeal papilloma.

The cases are presented in chronological order.

LKW. FEMALE, AGE 10 YEARS. HOARSE PAST SIX MONTHS. PAPILLOMA REMOVED ELSEWHERE WITHOUT BENEFIT.

Date Examined or Treated	Condition Found, Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
5-1-48	Right true cord and subglottic area; multiple papilloma on left side	Removed					
5-27-48	Anterior commissure	Removed					
6-23-48	Anterior ⅓ of right true cord	. . . .	. . . .		. . . .	. . . .	Diathermy
8-4-48	Left cord covered with papilloma	Removed	Penicillin	50,000 U.	4 × day	2 days	Diathermy
9-14-48	Right true cord	Removed					
11-19-48	Right true cord	Removed					
12-23-48	Right true cord	Removed					
1-19-49	No papilloma						

Patient was examined six more times at approximately six months intervals; no papilloma found.

Time covered by this record: 4 years. Age when last seen: 14 years. Condition when last seen: voice normal; larynx clear.

AVO, FEMALE, AGE 4 YEARS. HOARSE PAST TWO YEARS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
2-2-49	Large papilloma on right true cord	Removed					
2-5-49	. . . .	Tracheotomy					
3-31-49	Right true cord	Removed					
6-25-49	Larynx clear	. . . .					
8-15-50	Cords covered with papilloma	Removed	Penicillin S-R	200,000 U.	2 × day	2 days	
3-7-51	Hoarse; right true cord	Removed					
4-27-51	Left true cord	Removed	Aureomycin	150 mgs.	4 × day	5 days	Podophyllum,
6-19-51	No recurrence	. . . .					10%
9-21-51	Middle ⅓ both true cords	Removed	Aureomycin then	200 mgs. 50 mgs.	4 × day 4 × day	2 days 2 days	Diathermy to right Podophyllum,
11-16-51	No recurrence	. . . .					10%, to both cords
1-2-52	Slight return, bilat.	Removed	Penicillin S-R Aureomycin	1 cc. 100 mgs.	2 × day Every 5 hrs.	2 days 2 days	
5-2-52	Ant. ⅓ left cord	Removed	Penicillin	400,000 U.	Daily	2 days	
4-9-53	No papilloma; granulation tissue on posterior ⅓ of left true cord						

Time covered by this record: 4 years. Age when last seen: 6 years. Condition when last seen: considerably improved; no papilloma.

JH, FEMALE. AGE 3 YEARS. HOARSENESS AND DYSPNEA.

Date Examined or Treated	Condition Found, Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
7-30-49	Ant. commissure and left true cord	Removed	Penicillin Crysticillin	25,000 U. 1 cc.	Every 3 hrs. Daily	2 days 2 days	Followed by
8-22-49	Right true cord, ant.	Removed					
10-29-49	Right true cord	Removed					
12-7-49	Left cord	Removed					
2-14-50	Right cord	Removed					
2-16-50	. . . .	. . . .	Penicillin S-R	1 cc.	Daily	1 week	
4-28-50	Left true cord	Removed					
6-19-50	Poor airway	Tracheotomy	Aureomycin	150 mgs.	2 × day	3 weeks	
6-28-50	Both cords	Removed					
10-3-50	Both cords	Removed	Aureomycin	125 mgs.	4 × day	5 days	
11-21-50	Both false cords	Removed	Aureomycin	125 mgs.	4 × day	10 days	
1-29-51	Many on left false cord; few on right, also on ant. commissure	Some removed	Aureomycin	125 mgs.	4 × day	15 days	
4-19-51	Greatly improved	. . . .	Aureomycin	150 mgs.	4 × day	21 days	
8-9-51	Improvement continues; voice good	Closed tracheotomy					
11-28-51	Few on right ventricle and ant. commissure	Removed	Aureomycin	125 mgs.	4 × day	12 days	
4-14-52	Small papilloma on both true cords	Removed					
1-20-53	Small papilloma on left true cord and ant. commissure	Removed	Penicillin	400,000 U.	Daily	7 days	
4-22-53	Clear	. . . .					
5-20-55	No recurrence; voice good	. . . .					

Time covered by this record: approximately six years. Age when last seen: 9 years. Condition when last seen: larynx clear; voice normal.

CJW, MALE. AGE 3 YEARS. WEAK VOICE SINCE BIRTH AND "CHOKING SPELLS" PAST TWO MONTHS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
8-13-49	Both true cords covered with papilloma	Removed					
9-2-49	Both true cords, but left worse	Removed from left					
9-21-49	Ant. ½ left cord	Removed					
3-17-50	Multiple on both false cords and on left true cord	Removed	Penicillin S-R	1 cc.	Daily	3 days	
4-10-50	Left true and false	Removed	Penicillin	400,000 U.	Daily	3 days	
8-21-50	No recurrence	. . . .					
12-15-50	No recurrence	. . . .					
2-16-51	No recurrence	. . . .					
9-28-51	No recurrence	. . . .					

Time covered by this record: approximately 2 years. Age when last seen: 5 years. Condition when last seen: larynx clear, airway normal, and voice satisfactory.

LL, FEMALE. AGE 44 YEARS. HOARSE SINCE CHILDHOOD.

Date Examined or Treated	Condition Found, Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
7-20-50	Multiple, bilat.	Left cord stripped					
8-2-50	. . . .	. . . .	Penicillin	400,000 U.	Daily	2 days	
8-21-50	Left cord worse than right	Removed from left	Penicillin	400,000 U.	Daily	2 days	
3-20-51	Ant. ⅓ left cord, but smaller	Removed					
11-12-51	Small papilloma on ant. left cord	Removed					
10-15-53	No papilloma	. . . .					
5-12-54	No papilloma	. . . .					
3-21-55	No papilloma	. . . .					

Time covered by this record: more than four years. Age when last seen: 48 years. Condition when last seen: larynx clear; voice improved

SKS, FEMALE. AGE 3 YEARS. HOARSE SINCE AGE OF 18 MONTHS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
9-29-49	Left true cord, posterior ⅔	Removed	Crysticillin	100,000 U.	Daily	5 days	
6-23-50	Left true and false	Removed	Aureomycin	250 mgs.	4 × day	3 days	
10-13-50	Both cords	Removed	Aureomycin	250 mgs.	4 × day	4 days	
12-28-50	Voice better	. . . .					
4-5-51	Larynx filled with papilloma	Removed	Aureomycin	250 mgs.	4 × day	3 days	
5-11-51	Right cord, post., and ant. commissure	Removed	Penicillin	400,000 U.	2 × day	2 days	
10-10-51	Moderate recurrence	Removed	Aureomycin	250 mgs.	4 × day	2 days	
11-29-51	Very small papilloma ant. ⅓ both true cords		Penicillin	400,000 U.	Daily	2 days	
5-6-52	. . . .	T & A					
8-12-52	Voice excellent Larynx clear	. . . .					
11-1-52	Larynx clear	. . . .					
5-5-53	Larynx clear	. . . .					
11-3-53	Larynx clear	. . . .					
5-8-54	Larynx clear	. . . .					
9-15-54	Larynx clear	. . . .					
2-3-55	Larynx clear	. . . .					

Time covered by this record: approximately six years. Age when last seen: 9 years. Condition when last seen: excellent.

GA, FEMALE. AGE 2 YEARS. DYSPNEA FOR THREE WEEKS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
1-21-50	Left cord covered	Tracheotomy	Penicillin	30,000 U.	8 × day	7 days	
1-29-50	. . . .	Removed					
2-8-50	Growths returned	Removed	Penicillin	25,000 U.	8 × day	1 day	
4-21-50	Cords, bilat., and ant. commissure	Removed	Penicillin	20,000 U.	8 × day	1 day	
5-4-50	Growths returned						Electric needle
6-9-50	Right true cord	Removed					
7-15-50	Right true and false cords	Removed	Aureomycin	250 mgs.	4 × day	2 months	
9-18-50	No papilloma	. . . .					
11-17-50	Left true cord	Removed					
1-21-51	Right arytenoid	Removed	No antibiotic because of history of rash after last med.				
6-15-51	No papilloma	. . . .					
8-22-51	No papilloma						
9-22-52	Ant. commissure, small papilloma	. . . .	Aureomycin Spersoids	250 mgs. in milk	4 × day	3 weeks	
11-30-53	No papilloma	. . . .					
7-28-55	Appeared normal						

Time covered by this record: Five and one-half years. Age when last seen: 7 years. Condition when last seen: larynx clear; breathing normal.

JHE, FEMALE. AGE 35 YEARS. HOARSE FOUR MONTHS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
3-31-50	Middle ⅓ right cord, ant. ⅓ left cord, and ant. commissure	Removed					
6-6-51	Slight return	Removed	Aureomycin	250 mgs.	4 × day	1 week	
7-12-51	Normal	. . . .					
10-22-51	Ant. ⅗ of both true cords	Removed					Podophyllum, 10%, one application
11-19-51	Ant. ⅓ left cord	Removed					
12-10-51	No recurrence	. . . .					

Time covered by this record: approximately 15 months. Age when last seen: 36 years. Condition when last seen: larynx clear and voice normal.

Note that there had already been longer intervals of freedom from symptoms, followed by recurrence, than that last recorded. This patient was lost to follow-up.

DB, MALE. AGE 6 YEARS. HOARSE SINCE AGE OF SIX MONTHS.

Date Examined or Treated	Condition Found, Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
5-20-50	Both true cords and anterior commissure	Removed					
6-15-50	Growths returned	Removed	Aureomycin	250 mgs.	4 × day	3 days	
8-5-50	Growths returned	Removed					
12-11-50	Growths returned	Removed	Aureomycin	125 mgs.	4 × day	3 days	
3-26-51	Growths returned	Removed					
4-4-51	Growths returned	Removed	Aureomycin	250 mgs.	4 × day	5 days	
5-9-51	Growths returned	Removed	Aureomycin	250 mgs.	4 × day	5 days	
8-25-51	Airway very poor	Tracheotomy	Aureomycin	100 mgs.	6 × day	6 days	
8-31-51	Improved	. . . .	Aureomycin	125 mgs.	4 × day	22 days	
9-6-51	Continued improvement	. . . .	Aureomycin				
10-29-51	Status quo	Removed	Aureomycin	150 mgs.	4 × day	26 days	
2-7-52	Only slight return	Removed	Aureomycin	100 mgs.	4 × day	4 days	
3-14-52	Greatly improved	. . . .					
4-11-52	Continued improvement	. . . .					
5-20-52	Slight return	Removed	Aureomycin Spersoids	4 cc.	2 × day	4 days	
6-26-52	Left cord clear	. . . .					
8-12-52	No papilloma seen	. . . .					
9-30-52	Return on right side	Removed	Aureomycin Spersoids	2 cc.	3 × day	7 days	
12-5-52	No papilloma seen	. . . .					
4-10-53	Slight return	. . . .	Penicillin S-R	400,000 U.	Daily	4 days	
5-19-53	Ant. commissure and left false cord	Removed	Aureomycin Spersoids	4 cc.	2 × day	4 days	
11-8-54	Growths returned	Removed					
3-19-55	Growths returned	Removed					
7-18-55	Growths returned	Removed					

Time covered by this record: approximately five years. Age when last seen: 11 years. Condition when last seen: larynx badly scarred; growths recurrent.

JLP, FEMALE. AGE 2 YEARS. HOARSE SINCE AGE 6 MONTHS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
7-20-50	Both true cords and right false cord	Removed					
8-10-50	Severe dyspnea	Tracheotomy	Penicillin	200,000 U.	2 × day	6 days	
9-9-50	. . . .	Removed	Aureomycin	50 mgs.	3 × day	8 days	
10-6-50	Growths returned	Removed	Aureomycin	150 mgs.	2 × day	10 days	
11-14-50	One on right, few small ones on left	Removed	Aureomycin	150 mgs.	4 × day	4 days	
12-4-50	Much improved; few on right ant. true cord	. . . .	Aureomycin	150 mgs.	4 × day	4 days	
2-19-51	Returned, both true cords and right false	Removed					One application of podophyllum, 10%
4-21-51	Many on left, few on right	Removed					
5-17-51	Returned on right side	Removed					
7-20-51	Glottis almost closed	Removed, right					
7-24-51	. . . .	Removed, left					
9-21-51	Returned on both sides	Removed, right					
9-29-51	. . . .	Removed, left					
10-17-51	Returned, but fewer	. . . .	Chloromycetin	100 mgs.	4 × day	3 days	
11-10-51	Returned, few more	Removed	Penicillin	400,000 U.	Daily	2 days	
11-21-51	Returned, but fewer	Removed					
12-12-51	Returned, but fewer	. . . .	Penicillin	400,000 U.	Daily	2 days	
12-27-51	Further extension	. . . .	Penicillin	400,000 U.	Daily	2 days	
2-12-52	Status quo	Removed	Aureomycin	100 mgs.	4 × day	2 days	
3-12-52	Left true cord and interarytenoid fold	Removed	Aureomycin	50 mgs.	4 × day	2 days	

Continued on Next Page

JLP, CONTINUED.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
5-7-52	Both cords	Removed	Aureomycin	100 mgs.	4 × day	2 days	
5-28-52	Clearer; left false cord only	Removed	Aureomycin	100 mgs.	4 × day	2 days	
6-19-52	Few on both false cords	Removed					
7-25-52	Left side, true and false cords	Removed					
11-5-52	Posterior surface of epiglottis	Removed	Penicillin S-R	1 cc.	Daily	3 days	
1-5-53	Right false cord	Removed	Aureomycin Aureomycin	250 mgs. 250 mgs.	. . . . 4 × day	1 day, then 2 days	
1-21-53	Left true cord	Removed	Aureomycin	250 mgs.	4 × day	2 days	
2-25-53	Posterior right true cord	Removed	Aureomycin	250 mgs.	4 × day	3 days	and Podophyllum 10%, one application
3-26-53	Mid portion of right false cord; clearer than at any previous time	Removed	Aureomycin*	125 mgs.	4 × day	2 days	
5-20-53	Bilateral, but very small	Removed		125 mgs.	4 × day	2 days	
6-4-53	Left false cord	Removed	Aureomycin	50 mgs.	4 × day	2 days	
6-19-53	Improved; few small growths left false cord and epiglottis	Removed,					
7-15-53	Middle ⅔ of both cords	Removed					
8-11-53	Both cords	Removed, right					
9-2-53	None seen	. . . .					
10-2-53	Right true cord	Removed					

* Cardiac arrest; chest opened and heart massaged.

Continued on Next Page

JLP, CONTINUED.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
10-10-53	. . . .	. . . .	Crystalline Penicillin	1,200,000 U. 400,000 U. 50,000 U.	First day Daily 4 × day	 2 days 4 days	
11-20-53	Both false cords	Removed					
1-9-54	Both false cords	Removed					
2-12-54	Upper surface both cords and floor of ventricle	Removed					Podophyllum, 10%, one application
3-26-54	Multiple, bilat.	Removed	Penicillin	600,000 U.	Daily	2 days	
8-26-54	No papilloma seen	. . . .					
6-3-54	True and false cords, left side	Removed					
7-7-54	Ant. ⅓ left true cord, only	Removed					
10-22-54	Both cords	Removed					
11-10-54	Both cords	Removed					
1-26-55	Both cords	Removed					
2-23-55	Small, post. right true cord, only	Removed					
5-20-55	Left side clear; small on right	Removed	Penicillin S-R	600,000 U.	Daily	2 days	

Time covered by this record: Approximately five years. Age when last seen: 7 years. Condition when last seen: Greatly improved, but growths still recurrent.

DS, FEMALE. AGE 18 YEARS. HOARSE FOUR YEARS, AND PAPILLOMA REMOVED ELSEWHERE NINE TIMES SINCE 1948.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
10-3-50	Ant. of left true cord, ant. commissure, and a few on right side	Removed	Aureomycin	250 mgs.	4 × day	3 days	
12-1-50	True cords normal	. . . .					
2-7-51	Ant. left true cord	Removed					
2-24-51	Left ventricle and left true cord	Removed	Penicillin	400,000 U.	Daily	4 days	
2-30-51	. . . .	. . . .	Aureomycin	250 mgs.	4 × day	5 days	
1-20-53	Hoarse; growth on epiglottis; has been free since last admission until Oct., 1952	Removed					
5-19-53	Left cord and epiglottis	Removed	Aureomycin	250 mgs.	4 × day	6 days	
12-16-54	Ant. left cord	Removed					
5-2-55	No gross papilloma	. . . .					

Time covered by this record: approximately five years. Age when last seen: 23 years. Condition when last seen: no gross papilloma; voice good.

ML, MALE. AGE 2 YEARS. HOARSE AND DYSPNEIC.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
1-5-51	Entire glottic chink filled with papilloma	Cords were stripped	Aureomycin	125 mgs.	4 × day	5 days	
2-5-51	Left cord free, but return on right	Removed	Aureomycin	125 mgs.	4 × day	3 days	Podophyllum, 10%, one application
4-2-51	Recurrence, but to lesser degree	Removed					
Patient did not return.							

Time covered by this record: Three months. Age when last seen: 2 years. Condition when last seen: improved.

BAW, FEMALE. AGE 22 YEARS. HOARSE THREE WEEKS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
7-23-51	Ant. ½ both cords	Removed	Aureomycin	150 mgs.	4 × day	3 days	
8-10-51	Upper surface left true cord	Removed	Aureomycin Penicillin S-R	150 mgs. 400,000 U.	4 × day Daily	3 days 3 days	
9-6-50	Right true cord	Removed	Penicillin S-R	200,000 U.	Daily	3 days	
9-20-51	Much improved; small papilloma on right true cord	Removed	. . . .	. . . .	. . . .	. . . .	One application of podophyllum, 10%
10-4-51	Right cord	. . . .	Penicillin	200,000 U.	Daily	2 days	Electric cautery
10-25-51	Multiple, both cords	Removed	Aureomycin	100 mgs.	4 X day	2 days	. . . .
11-21-51	Entire length of left true cord	. . . .	Penicillin S-R	100,000 U.	Daily	2 days	Electric cautery
12-3-51	On both false cords; remainder of larynx now clear	Removed	Penicillin S-R	200,000 U.	Daily	2 days	
2-12-54	No papilloma	Examined only					

Time covered by this record: Approximately two and one-half years. Age when last seen: 25 years. Condition when last seen: larynx clear for two months.

GWR, MALE. AGE 9 YEARS. HOARSENESS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
8-3-53	Both cords and epiglottis covered	Removed					
12-29-53	Growths returned	Removed					
7-31-54	Growths returned	Removed					
12-20-54	Growths returned	Removed					
1-9-55	Growths returned	Removed					
1-19-55	Growths returned	Removed	Terramycin	125 mgs.	4 × day	3 days	
4-20-55	Ant. ⅓ left true cord, only	Removed					

Time covered by this record: Approximately 2 years. Age when last seen: 11 years. Condition when last seen: Greatly improved.

MH, FEMALE. AGE 41 YEARS. HOARSE FOR 10 YEARS.

Date Examined or Treated	Condition Found. Location of Growths	Surgical Procedures	Antibiotics Given	Dosage	Frequency	Duration	Other Treatment
5-1-53	Both true cords covered with papilloma	Removed					
6-12-53	Growths returned	Removed	Penicillin	400,000 U.	4 × day	3 days	
7-15-53	No recurrence	. . . .					
Patient did not return.							

Time covered by this report: 10 weeks. Age when last seen: 41 years. Condition when last seen: Improved.

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ANNOUNCEMENT.

The Mount Sinai Hospital, New York, in affiliation with Columbia University announces an intensive postgraduate course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty given by Irving B. Goldman, M.D., and staff, July 14, 1956, to July 28, 1956. Candidates should apply to Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, 5th Avenue and 100th Street, New York 29, New York.

PULSION DIVERTICULUM OF THE HYPOPHARYNX.*†

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D. M. LIERLE, M.D., and
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Experience in the management of pulsion diverticulum of the hypopharynx in a series of 25 patients (1950-1955) has indicated that one-stage diverticulectomy is applicable in most patients. The method is safe in appropriate cases if a proper anatomical approach is utilized, and if the pharyngeal closure is secure and is accomplished without tension. Suspension of the sac and the two-stage excision is indicated in ill and malnourished patients, in the presence of inflammation and edema of the sac or following instrumental perforation of the diverticulum.

CLINICAL OBSERVATIONS.

Pulsion diverticulum of the hypopharynx is a protrusion of mucosal and submucosal layers of the pharynx through Killian's dehiscence[1] (between transverse fibers of the cricopharyngeus and oblique fibers of the inferior pharyngeal constrictor) into the posterior mediastinum. The most attractive theory of origin postulates incoordination of deglutition, with failure of the cricopharyngeus to relax in a manner appropriate to the second phase of swallowing. The weakest area of the pharynx (Killian's dehiscence) would be especially vulnerable to the abnormally increased intrapharyngeal pressure thus produced. Protrusion and diverticulum formation would be expected in this area of weakness, especially in the elderly.

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Twenty-one of this group of 25 patients were over the age of 60, and of these 18 were edentulous. The infrequency of occurrence of pulsion diverticula even in the edentulous, however, would suggest that poor mastication of food is not an important causative factor. Difficulty in swallowing is a common early symptom of these patients, but it is difficult to establish this symptom clearly as preceding the development of the sac. Three patients of this group on Roentgenologic study of a barium swallow had delay of entry of barium into the stomach. This might be evidence of incoordination of esophageal function. Though pulsion diverticula occur at a site of congenital weakness in the pharyngeal wall, they are considered to be acquired diverticula because their walls consist of only two of the three layers of the parent viscus (pharynx). We have seen only two examples of congenital diverticula and these were in newborn infants.[2]

The symptoms of pulsion diverticulum are related to the size of the hernial sac. When the sac is small the usual complaint is that of food sticking in the throat. When the sac is of moderate size it becomes dependent in position, fills easily with ingested material and leads to regurgitation. The very large diverticula fill with food and distort the hypopharynx and compress the esophagus, making it impossible for the patient to swallow an adequate amount of food. Malnutrition becomes increasingly more serious.

Lahey[3] proposed classification of these sacs into Stage I, Stage II and Stage III according to size and symptoms (see Fig. 1). The small (Stage I) sacs may annoy the patient, but they are not dangerous. The Stage II diverticula cause distressing regurgitation and gurgling and may be responsible for bronchitis or pneumonitis from inadvertent aspiration of contents of the sac. In Stage III sacs, malnutrition is added to the other difficulties.

Another hazard associated with the diverticula is possible instrumental perforation of the sac during diagnostic esophagoscopy or intubation. Great caution is necessary to avoid injury during this procedure. The esophagoscope passes easily into a large sac and the narrow slit-like aperture of the

esophagus anterior to the large diverticular mouth is difficult to visualize. At times it is impossible to advance the instrument into the esophageal lumen. Mediastinitis may result from mucosal laceration without gross perforation of the diverticulum. A preliminary esophagram will establish the diagnosis of pulsion diverticulum and forewarn the endoscopist. Two patients in this series entered the hospital with mediastinitis following esophagoscopy. The first (T.B. No.

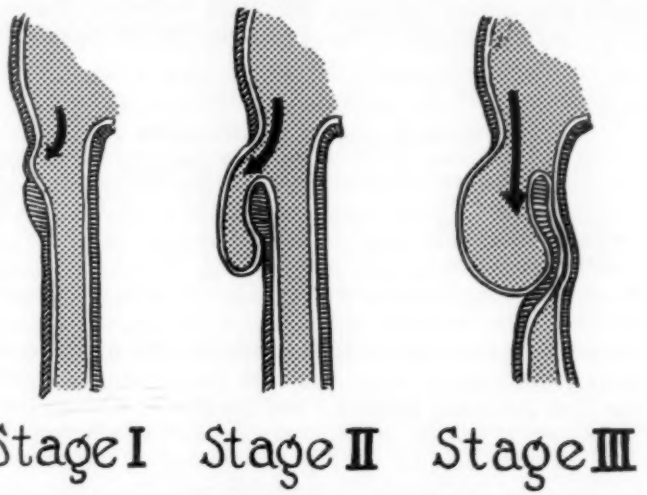

Fig. 1. Diagram illustrating the three stages. Stage I is symptomatic but does not interfere with swallowing or nutrition. Stage II may cause annoying symptoms and be associated with regurgitation. Stage III as illustrated is likely to be associated with mechanical interference with swallowing and resultant malnutrition.

50-12190) was admitted five days following endoscopic perforation of the sac. He was treated by drainage of the posterior mediastinum and suspension of the sac, and he recovered. The second (P.H. No. 52-4198) was moribund from mediastinitis at the time of his readmission to the hospital three days following diagnostic esophagoscopy during which there was no gross perforation of the sac. He died the same day.

Esophagoscopy is indicated preoperatively to remove solid material from the sac and to determine whether the sac is inflamed or ulcerated. A liquid diet is given before operation. In case of dehydration, appropriate fluid therapy is instituted. Transfusions of whole blood may be required if a lowered blood volume has resulted from malnutrition. Antibiotics are administered before operation if the diverticulum is inflamed or if there is pneumonitis.

Table I indicates the treatment carried out in the 25 patients seen during the years 1950-1955, inclusive. The stage of the sac is indicated in the same table. Sac extirpation was

TABLE I.

PULSION DIVERTICULA OF HYPOPHARYNX 1950-1955.

Treatment	Size (Stage) of Sac			Total
	I	II	III	
One stage excision	1	12	4	17
Two stage excision	0	0	1	1
Suspension of sac	0	1	1	2
Examination only	3	1	1	5
	4	14	7	25

refused or was not advised in five patients. Three of these had Stage I protrusions. It is seen that the one-stage operation was most commonly employed, and usually for a Stage II sac. Suspension of the sac or two-stage excision was indicated in three patients because of (a) perforation of the sac with mediastinitis, (b) severe malnutrition, and (c) inflammation of the sac. Though the one-stage procedure is ordinarily preferred, staged operations are indicated if there is a threat of infection, if the patient's nutritional state is so poor that tissue healing is likely to be impaired, or if there exists a contraindication to anything more than simple elevation of the tip of the diverticulum.

There were two postoperative deaths in this group of patients. One death (H.H. No. 17975) occurred shortly following one-stage diverticulectomy from cardiac arrest. The second death (O.T. No. 51-14208) was due to carcinoma of the colon, and followed recovery from the first stage (sac suspension) procedure. The late results of operation were satisfac-

tory. Recurrence of the diverticulum is known to have occurred in two patients (F.V. No. 50-10342 and D.S. No. 42-2764). In each patient the recurrent sac was small and non-symptomatic.

TECHNICAL CONSIDERATIONS.

Diverticulectomy is usually carried out under endotracheal anesthesia. In seriously ill patients, suspension of the tip of the sac by suture to the sternohyoid or sternocleidomastoid muscle can be accomplished with local and regional anesthesia.

Esophagoscopy is carried out in the operating room to make certain that the diverticulum is empty. At the same time, a Levine tube is threaded down the esophagus under direct vision if this can readily be done. If the Levine tube cannot be inserted before starting the operation, the anesthetist can easily introduce it after the diverticulum is mobilized and lifted cephalad. The excision and repair of the sac is carried out with the Levine tube in place. The tube may be removed at the termination of operation. It is left in place if there is indication for gastric or esophageal decompression, or need for early postoperative tube feeding.

Access to the posterior mediastinum is obtained through a transverse incision in skin at cricoid level. As this incision parallels lines of skin tension, it heals with minimal scarring, and the best possible cosmetic result is obtained. By placing the incision at this level, the level at which the neck of the diverticulum is located, and by elevating skin flaps in the plane between platysma myoides and deep cervical fascia, no restrictions are imposed upon deeper exposure. Deep fascia (Fascia colli) is incised along the anterior border of the sternocleidomastoid, extending as low as the clavicle if such exposure should appear to be required for the mobilization of a very large diverticulum. Approach is usually on the left side of the neck. After opening cervical fascia, the anterior infrahyoid muscles are retracted medially and the sternocleidomastoid muscle and the superior belly of the omohyoid are retracted laterally. As the lateral lobe of the thyroid gland is retracted forward and the carotid sheath lateralward,

alar fascia is tensed between visceral and vascular compartments of the neck. The middle thyroid vein is ligated and divided as it crosses alar fascia. A vertical incision in alar fascia between superior and inferior thyroid arteries exposes the posterior mediastinum. In case of difficult mobilization of a large diverticulum, the inferior thyroid artery may have to be divided to allow dissection deeper into the posterior mediastinum.

The diverticulum is mobilized so that it can be lifted up. Care is exercised to avoid injury to the recurrent laryngeal nerves which ascend to the larynx close to the neck of the sac. The sac consists of mucosa and attenuated aponeurosis of pharynx but may have some muscle fibers near its neck. Such muscle bundles are swept off the neck of the sac. Care is taken to avoid over-zealous dissection at this point, as it is possible to mobilize pharyngeal mucosa to the extent of creating serious constriction of the pharynx and at the same time to produce dangerous tension at the line of suture used to close the pharynx after sac excision. As a further precaution against undue tension a stump of diverticular neck about one-fourth inch long is preserved, as this much tissue will be required for two lines of suture.

Ordinarily, a clamp is placed transversely across the neck of the sac, the sac is excised, and a continuous fine catgut suture is run over the clamp at the innermost suture line. This suture includes mucosal and submucosal layers of the pharynx. This inner line is then buried with a row of interrupted Lambert sutures of fine silk, which are placed in the aponeurosis of pharynx. This closure is then reinforced with interrupted silk sutures in muscularis of pharynx.

A Penrose drain is placed to the posterior mediastinum and closure of deep cervical fascia, platysma and skin follows.

SUMMARY.

1. Twenty-five patients with pulsion diverticulum of the hypopharynx were seen during the years 1950-1955.

2. One stage diverticulectomy is preferred for most patients. A transverse skin incision is advantageous. By leav-

ing a one-fourth inch cuff of diverticular neck, secure closure is accomplished without tension and pharyngeal narrowing is avoided.

3. Sac suspension in the seriously debilitated or ill patient is the simplest and least hazardous procedure as a temporizing measure. Staged excision of the sac is indicated if there is local inflammation or severe malnutrition.

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2. BRINTALL, E. S., and KRIDELBAUGH, W. W.: Congenital Diverticulum of the Hypopharynx Simulating Atresia of the Esophagus. *Ann. Surg.*, 131:564:574, April, 1950.

3. LAHEY, FRANK H.: Esophageal Diverticula. *Surg. Clin. of N. A.*, 813-826, June, 1953.

UNIVERSITY OF ILLINOIS, COLLEGE OF MEDICINE.

The next Laryngology and Bronchoesophagology Course to be given by the University of Illinois, College of Medicine, is scheduled for the period November 5 through November 17, 1956. The course is under the direction of Dr. Paul H. Holinger.

Interested registrants will please write directly to the Department of Otolaryngology, University of Illinois, College of Medicine, 1853 W. Polk Street, Chicago 12, Ill.

SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY.

The meeting dates of the Sixth International Congress of Otolaryngology are again emphasized as May 5th through May 10th, 1957. The scientific program for the Plenary Sessions is now complete and is as follows:

CHRONIC SUPPURATION OF THE TEMPORAL BONE.

OPENERS: Marcus Diamant, Central County Hospital, Halmstad, Sweden—Anatomical Etiological Factors in Chronic Middle Ear Discharge.

Luzius Rüedi, Zurich, Switzerland—Pathogenesis and Treatment of Cholesteatoma in Chronic Suppuration of the Temporal Bone.

Horst Wullstein, Director, Otolaryngological Clinic, University of Würzburg, Germany—Surgical Repair for Improvement of Hearing in Chronic Otitis Media.

DISCUSSERS: A. Tumarkin, Liverpool, England; Juan Manuel Tato, Buenos Aires, Argentina; T. E. Cawthorne, London, England; Fritz Zöllner, Freiburg, Germany.

COLLAGEN DISORDERS OF THE RESPIRATORY TRACT.

OPENERS: Hans Selye, Director, Institute of Experimental Medicine and Surgery, University of Montreal, Faculty of Medicine, Montreal, Canada.

Introduction:

Michele Arslan, Padua, Italy—The Upper Respiratory Tract.

Leslie Gay, Physician-in-Charge, Allergy Clinic, The Johns Hopkins Hospital, Baltimore, U. S. A.—The Lower Respiratory Tract.

DISCUSSERS: Victor E. Negus, London, England; Branimir Gusic, Zagreb, Yugoslavia; Aubrey G. Rawlins, San Francisco, U. S. A.; Henry L. Williams, Rochester, Minn., U. S. A.

PAPILLOMA OF THE LARYNX.

OPENERS: Jo Ono, Tokyo, Japan—Etiology.

Plinio de Mattos Barretto, Faculty of Medicine, University of Sao Paulo, Brazil.

Diagnosis:

F. C. W. Capps, London, England—Therapy.

DISCUSSERS: C. A. Hamberger, Göteborg, Sweden; Pedro Hernandez Gonzalo, Havana, Cuba; Eelco Huizinga, Groningen, Netherlands; Albert von Riccabona, Vienna, Austria.

Applications to present voluntary papers are being received regularly and anyone wishing to present such a paper should make known his intentions prior to the deadline of Oct. 1, 1956.

The motion picture sessions, as well as the scientific exhibits, will prove to be outstanding in every respect. It is essential that anyone wishing to present an exhibit should make his intentions known immediately, as the final date for consideration is Aug. 1, 1956; applications to present motion picture films should be sent in before Oct. 1, 1956. Anyone planning to attend the Congress and who has not yet registered should do so immediately in order to obtain hotel registration priority.

For more detailed information pertaining to the Sixth International Congress please communicate with the General Secretary, 700 N. Michigan Ave., Chicago 11, Ill., U. S. A.

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES.

(Secretaries of the various societies are requested to keep this information up to date).

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Editor-Librarian: Dr. Henry L. Williams, Mayo Clinic, Rochester, Minn.
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Meeting: Statler Hotel, Washington, D. C., May 1957.

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Meeting:

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Meeting: Palmer House, Chicago, Ill., October 8-11, 1956.

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Annual Clinical Session: Illinois Masonic Hospital, Chicago, Illinois, October, 1956.
Annual Meeting: Palmer House, Chicago, Illinois, October, 1956.

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Meeting: Palmer House, Chicago, Ill., October, 1956.

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Time and Place:
President: Dr. J. H. Font, Medical Arts Bldg., San Juan, P. R.

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